CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S038

19-847/S024

19-857/S027

19-858/S021

20-780/S008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	19-537/S-038
Submission Date:	2/29/00
Drug:	Ciprofloxacin hydrochloride (Cipro®) tablets
Sponsor:	Bayer Corporation West Haven, CT
Type of Submission:	Efficacy supplement for the addition of the indication of inhalational anthrax (post-exposure)
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

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ON ORIGINAL

I. BACKGROUND

Anthrax is a bacterial infection, caused by a gram-positive rod, which has been recognized as a human pathogen causing cutaneous, gastrointestinal, and inhalational disease. These forms of infection with *Bacillus anthracis* have been traditionally associated with agricultural ~~or~~ industrial exposures. Today, human anthrax is rare in the United States though it remains an endemic disease in other areas of the world. Most recently, attention has turned to *B. anthracis* as a possible agent of biological warfare or bioterrorism.

The Bayer Corporation, responding to an expressed public health need, has submitted an application for the addition of the indication inhalational anthrax (post-exposure) to the label of Cipro® (ciprofloxacin). This is the first antimicrobial drug application submitted to the Food and Drug Administration (FDA) for an indication resulting from the intentional use of a biological agent. The approval of this indication will be based on the use of a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, under the accelerated approval regulations (21 CFR 314.510 subpart H).

Inhalational anthrax is an extremely rare disease. It cannot ethically be studied in human subjects under circumstances of intentional exposure. There are drugs with currently approved labeling by FDA for disease associated with *B. anthracis.* Labels for penicillin, tetracycline, doxycycline, and minocycline products list *B. anthracis* among the organisms susceptible to these agents. None of these agents is indicated specifically post-exposure for disease caused by inhaled *B. anthracis.*

Based on the *in vitro* activity of ciprofloxacin against this organism, the efficacy demonstrated in the prophylaxis of inhalational anthrax in Rhesus monkeys, and the concern about the possibility of the engineering of a strain that is resistant to penicillin and tetracycline, ciprofloxacin was recommended as a drug of choice for post-exposure prophylaxis by the CDC, Working Group for Civilian Biodefense (JAMA 1999;1735-45) and the 3rd Edition of the US Army Medical Research Institute of Infectious Diseases handbook "Medical Management of Biological Casualties."

The sponsor is submitting literature data to support this indication, including *in vitro* microbiology data and data from non-human primate (Rhesus monkey) models of infection. In addition, they have provided safety data gathered from previous use of ciprofloxacin in adults and pediatrics.

The proposed dosing recommendations are within the approved dosing range for adults. Although ciprofloxacin is not approved in pediatrics, there are safety data available from cystic fibrosis patients using daily doses of 30 mg/kg of ciprofloxacin. In addition, there are safety data on ciprofloxacin obtained through the FDA's Spontaneous Reporting System.

There are also long-term safety data in adults to cover the proposed duration of therapy for this indication. Two patient groups that received treatment with ciprofloxacin for > 30 days were identified (1) by literature search, and (2) by the sponsor's database pool. Data on the long-term safety in pediatrics are also included, but are limited to small numbers exposed.

II. INDICATION AND DOSAGES

Ciprofloxacin in tablet form was approved for human use in the US in 1987; the intravenous (IV) solutions were approved in 1990. Both are approved for a wide variety of indications. Dosing is specific to the approved indication, and ranges from 100-750 mg orally every 12 hours for the tablet. For the IV formulation, the approved dose ranges from 200 to 400 mg every 8 to 12 hours.

The proposed dosing regimens for ciprofloxacin for inhalational anthrax (post-exposure) are given below:

Patient Population	Oral dose	Intravenous dose
Adult	500 mg Q12h x 60 days	400 mg (not to exceed 800 mg) Q12h
Pediatric*	10-15 mg/kg (not to exceed 500 mg per dose) Q12h x 60 days	10-15 mg/kg Q12h (not to exceed 800 mg per day)

* For children greater than 45 kg, the adult dosage should be used

Therapy should be initiated immediately after suspected or confirmed exposure and continue for 60 days.

III. CLINICAL PHARMACOLOGY SYNOPSIS

What pharmacokinetic data are available from monkeys infected with inhalational anthrax?

The study of ciprofloxacin to prevent inhalational anthrax was performed in a non-human primate (macaque) model and is supported by *in vitro* data assessing the activity of ciprofloxacin against *B. anthracis*. The authors also measured peak and trough serum concentrations of ciprofloxacin after administration of doses calculated by extrapolation from human doses.

Kelly, et al. Serum Concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. Journal Infect Dis 1992;166:1184-7.

Note: The raw ciprofloxacin data from this study can be found in Appendix 1.

Male and female adult monkeys were studied with a mean body weight of 7.7 kg (range 5.1 to 13.0 kg), and a mean body surface area of 0.46 m^2 [redacted] This represents a mean of 26% of the 1.73 m^2 body surface area of a 65-kg, 170-cm human. Ten animals were exposed to aerosolized anthrax spores and received a single ciprofloxacin 250 mg dose per nasogastric tube (pngt) 24 hours following exposure, followed twelve hours later by ciprofloxacin 125 mg pngt every 12 hours for 30 days. Blood samples for measurement of peak ciprofloxacin concentrations were collected on Days 5, 9, 20, and 30. Trough concentrations were collected on Days 3, 5, 9, and 20.

None of 10 monkeys treated with ciprofloxacin died from anthrax within the 30-day treatment period. One monkey died on Day 5 from accidental injection of drug into the lung.

Figures 1 and 2 below present individual (mean ± SD) peak and trough blood levels of ciprofloxacin, respectively, for during the 30-day period of drug administration. The MIC_{90} of ciprofloxacin for *B. anthracis* is also presented.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

How does the exposure to ciprofloxacin in monkeys compare to humans?

Figures 3 and 4 (page 9) present individual (mean ± SD) serum or plasma concentrations of ciprofloxacin observed in the monkeys in the study performed by Kelly et al. compared with mean ± SD values obtained from the literature in a number of different human populations, including pediatrics. It should be noted that the pediatric data is derived from patients with cystic fibrosis (CF). It has been shown that the pharmacokinetics of ciprofloxacin in adult patients with CF are comparable to healthy adult subjects. Table 1 describes the populations and dosing regimens depicted in Figures 3 and 4.

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Table 5. Summary of Ciprofloxacin Pharmacokinetics from Various Literature Articles

Population	Dose/Regimen	Route	N	$C_{max,ss}$ (µg/mL) ± SD	$C_{min,ss}$ (µg/mL) ± SD	$AUC_{0-24,ss}$ (µg*h/mL) ± SD	Notes
Monkeys	250 mg x 1, then 125 mg po Q12h (*32 mg/kg x 1, then 16 mg/kg*)	PO	10	1.74 ± 1.41	0.17 ± 0.15	--	Loading dose of 2x used for 1st dose
Adults	500 mg Q12h (*7.1 mg/kg*)	PO	12	2.89 ± 0.54	0.28 ± 0.13	27.9 ± 5.72	At steady state
Adults	400 mg Q12h (*5.6 mg/kg*)	IV	--	4.56	0.2	25.4	At steady state
Human Males	400 mg x 1 (*5.6 mg/kg*)	IV	11	3.11 ± 0.61*	--	9.27 ± 1.51*	*Single dose, not at steady state
Obese Human Males	400 mg x 1 (*3.6 mg/kg*)	IV	17	2.66 ± 0.53*†	--	7.72 ± 1.49*	*Single dose, not at steady state
Peds, CF	10 mg/kg Q8h	IV	18	5.0 ± 1.5	0.39 ± 0.18	24.0 ± 6.4	Q8h dosing; different from proposed regimen
Peds, CF	20 mg/kg Q12h	PO	18	3.7 ± 1.4	0.42 ± 0.21	36.6 ± 12.0	Total dose 40 mg/kg; higher than proposed regimen
Peds, CF	10 mg/kg Q12h	IV	10	8.3	[redacted]	31.4	Similar to proposed regimen; levels obtained after 2nd IV dose (30 min infusion)
Peds, CF	15 mg/kg Q12h	PO	8	3.5	--	27.0	Similar to proposed regimen; levels obtained after 1st oral dose and preceded by two IV doses of 15 mg/kg over 30 min

CF- cystic fibrosis

†The C_{max} obtained after a single dose in obese human males is similar to that obtained after multiple dosing in adults of ideal body weight

Figure 3. Ciprofloxacin peak concentrations-animal and human studies

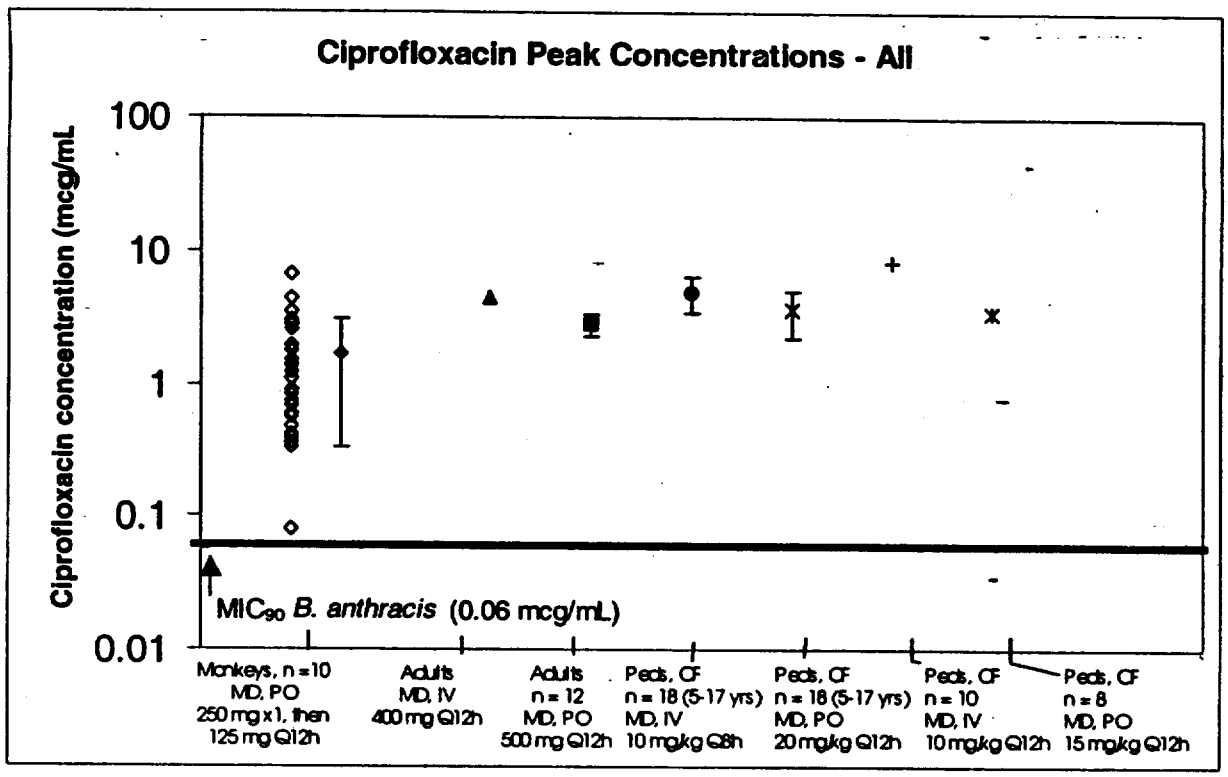
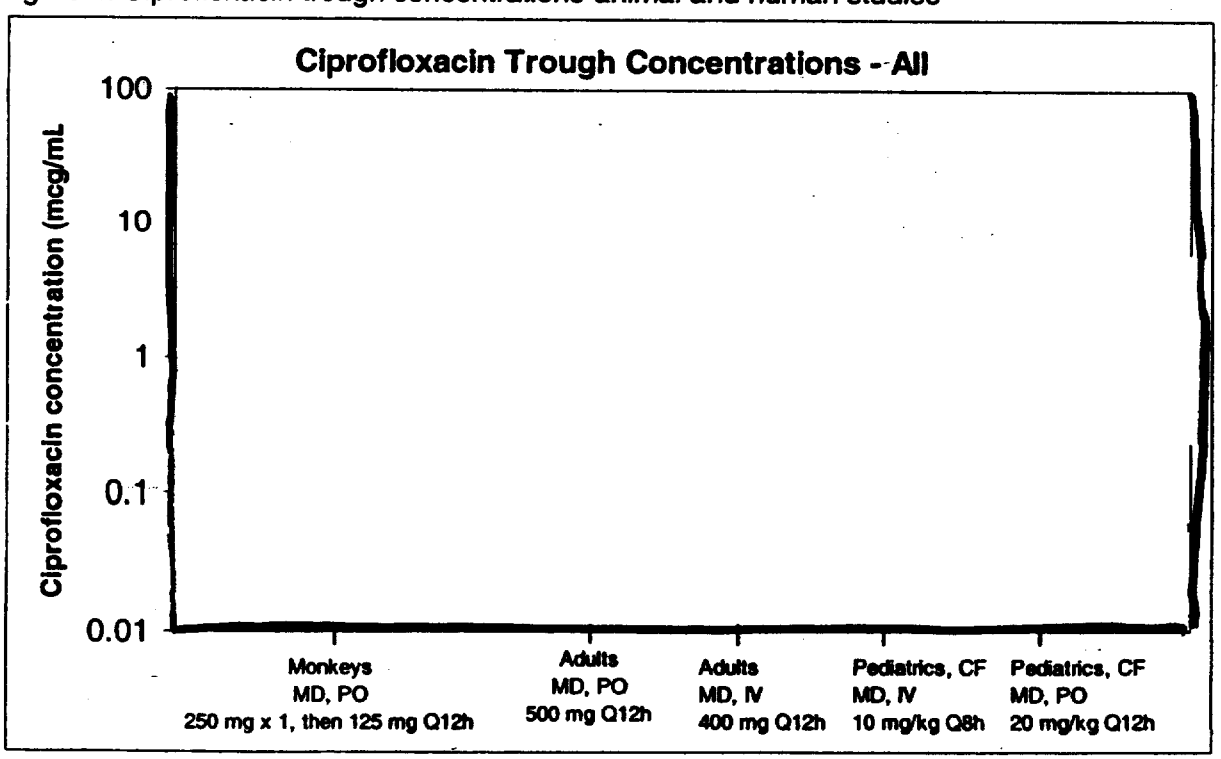


Figure 4. Ciprofloxacin trough concentrations-animal and human studies



Is there a pharmacokinetic/pharmacodynamic (PK/PD) relationship between ciprofloxacin exposure and efficacy in inhalational anthrax?

Fluoroquinolones, including ciprofloxacin, demonstrate concentration-dependent killing. The goal of a dosing regimen for these drugs is to maximize the serum concentrations. The peak concentration (C_{max})/MIC and/or AUC/MIC ratios are considered PK/PD parameters that best correlate with drug efficacy. Better correlation has been found with the AUC/MIC ratio than C_{max}/MIC, except possibly in infections where there is a significant risk of the emergence of resistant organisms. The relationship between these PK/PD parameters and drug efficacy has been demonstrated in animals models of infection as well as some clinical trials. Much of these data are derived from studies of infections with extracellular gram-negative organisms and in patients with nosocomial infections. Some recent data have demonstrated the usefulness of the AUC/MIC ratio for *Streptococcus pneumoniae*.

A comparison of pharmacokinetic with pharmacodynamic parameters in an animal model or human infection with inhalational anthrax cannot be made. *Bacillus anthracis* is gram-positive organism that exists intracellularly, so the optimal AUC/MIC or peak/MIC ratio is not known. In addition, there have been no prospective studies performed that link clinical outcome to drug exposure for this infection. However, in general when there is a demonstrated relationship between plasma concentrations of drug and response, pharmacokinetic data can be used as one way to characterize drug efficacy. Because of the unsuitability of performing a clinical trial in this particular infection, an alternative is to link the extent of ciprofloxacin systemic exposure in the animal model to what is seen in humans. As shown in Figures 3 and 4, the pharmacokinetics of ciprofloxacin in monkeys and humans are similar.

IV. GENERAL COMMENTS (NOT TO BE FORWARDED TO THE SPONSOR)

1. The sponsor has proposed a ciprofloxacin dose range of 10-15 mg/kg every 12 hours for pediatric patients treated with either IV or oral ciprofloxacin. In adults, a 500 mg oral dose given every 12 hours has been shown to produce an AUC equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 12 hours. In an ongoing study in pediatric patients with complicated urinary tract infections, ciprofloxacin is being initiated at a dose of 10 mg/kg IV every 12 hours, followed by 10-20 mg/kg orally every 12 hours.

   Therefore, the pediatric dosing recommendations for inhalational anthrax (post-exposure) will be modified, such that the IV dose will be 10 mg/kg infused over 60 minutes every 12 hours and the oral dose will be 15 mg/kg every 12 hours. Ciprofloxacin peak and trough concentrations obtained from pediatric patients administered this regimen, are consistent with what is seen in adults following 500 mg orally or 400 mg IV every 12 hours and are similar or in excess of the ciprofloxacin concentrations associated with survival in the monkey model.

V. LABELING RECOMMENDATIONS

1 page(s) of revised draft labeling has been redacted from this portion of the review.

VI. RECOMMENDATION

Based on what is known of the clinical pharmacology of ciprofloxacin, the clinical pharmacology/biopharmaceutics section of NDA 19-537/S-038 is acceptable and adequate to support approval.

/S/ 8/30/00

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) /S/ 8/30/00

OCPB Briefing July 27, 2000 (attendees): Arzu Selen and Funmi Ajayi

cc: HFD-590: /NDA 19-537; SLR-038
/PM/JensenV
/MOTL/RocaR
/MO/MeyerhoffA
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ
HFD-205: FOI

APPENDIX 1: Ciprofloxacin Pharmacokinetic Monkey Data (Kelly et al 1992)

Cipro Trough - Monkeys

Monkey ID	Day 3	Day 5	Day 9	Day 20
82A35	0.1	0.07	0.08	0.08
358D	0.22	0.1	0.1	0.23
B7388	0.1	0.1	0.08	0.12
T292	0.42	0.43		
410D	0.08	0.07	0.05	0.04
A32	0.18	0.22	0.16	0.06
45Y	0.13	0.1	0.26	0.05
84456A	0.18	0.21	0.16	0.1
T308	0.45	0.31	0.27	0.83
40B	0.2	0.07	0.08	0.08
RANGE MIN				
MAX	0.45	0.43	0.27	0.83
GEOMEAN	0.18	0.14	0.12	0.11
MEAN	0.21	0.17	0.14	0.18
STDDEV	0.13	0.12	0.08	0.25

Cipro Peak - Monkeys

Monkey ID	Day 5	Day 9	Day 20	Day 30
82A35	0.91	0.56	0.39	0.39
358D	6.7	1.4	2.91	0.36
B7388	1.8	2.6	3.09	1.11
T292				
410D	0.08	2.6	3.57	1.8
A32	0.48	0.42	0.33	1.23
45Y	0.84	1.56	0.75	2.94
84456A	0.39	0.69	1.41	0.6
T308	1.98	2.91	4.47	1.56
40B	3.12	1.38	2.58	2.82
RANGE MIN				
MAX	6.7	2.91	4.47	2.94
GEOMEAN	0.98	1.29	1.55	1.12
MEAN	1.81	1.57	2.17	1.42
STDDEV	2.07	0.94	1.50	0.96

Reviewer's Comment: The mean ciprofloxacin concentrations achieved following dosing to steady state (expected C_{max} and trough) expressed in the label are based on a calculation of the geomentric mean as performed by the investigators (Kelly et al 1992). The numbers above were obtained from the raw data sheets and are slightly different due to difficulties in deciphering the numbers.

Steady State Parameters	*Geometric Mean Values (µg/mL)*	
	Kelly et al	*Reviewer's Analysis*
Expected C_{max}	*0.98 – 1.69*	*0.98 – 1.55*
Trough	*0.12 – 0.19*	*0.11 – 0.18*

APPENDIX 2: Literature Reference List

1. Gonzales MA, Uribe F, Moisen SD, et al. Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother 1984;26:741-4.

2. Peltola H, Ukkonen P, Saxen H, et al. Single-dose and steady-state pharmacokinetics of a new oral suspension of ciprofloxacin in children. Pediatrics 1998;101:658-62.

3. Rubio TT, Miles MV, Lettieri JT, et al. Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbation. Pediatr Infect Dise J 1997;16:112-7.

4. Schaefer HG, Stass H, Wedgwood J, et al. Pharmacokinetics of ciprofloxacin in pediatric cystic fibrosis patients. Antimicrob Agents Chemother 1996;40:29-34.

5. Peltola H, Vaarala M, Renkonen OV, et al. Pharmacokinetics of single-dose oral ciprofloxacin in infants and small children. Antimicrob Agents Chemother 1992;36:1086-90.

6. Schaad UB, Salam MA, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr Infect Dis J 1995;14:1-9.

7. Allard S, Kinzig M, Boivin G, et al. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Thery 1993;54:368-73.

8. Neuman M. Clinical pharmacokinetics of the newer antibacterial 4-quinolones. Clin Pharmacokinet 1988;14:96-121.

9. Davis RL, Koup JR, Williams-Warren J, et al. Pharmacokinetics of ciprofloxacin in cystic fibrosis. Antimicrob Agents Chemother 1987;31:915-9.

10. Reed MD, Stern RC, Myers CM, et al. Lack of unique ciprofloxacin pharmacokinetic characteristics in patients with cystic fibrosis. J Clin Pharmacol 1988;28:691-9.

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	19-847/S-024
Submission Date:	2/29/00
Drug:	Ciprofloxacin (Cipro®) IV Solution Vials
Sponsor:	Bayer Corporation West Haven, CT
Type of Submission:	Efficacy supplement for the addition of the indication of inhalational anthrax (post-exposure)
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

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I. BACKGROUND

Anthrax is a bacterial infection, caused by a gram-positive rod, which has been recognized as a human pathogen causing cutaneous, gastrointestinal, and inhalational disease. These forms of infection with *Bacillus anthracis* have been traditionally associated with agricultural or industrial exposures. Today, human anthrax is rare in the United States though it remains an endemic disease in other areas of the world. Most recently, attention has turned to *B. anthracis* as a possible agent of biological warfare or bioterrorism.

The Bayer Corporation, responding to an expressed public health need, has submitted an application for the addition of the indication inhalational anthrax (post-exposure) to the label of Cipro® (ciprofloxacin). This is the first antimicrobial drug application submitted to the Food and Drug Administration (FDA) for an indication resulting from the intentional use of a biological agent. The approval of this indication will be based on the use of a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, under the accelerated approval regulations (21 CFR 314.510 subpart H).

Inhalational anthrax is an extremely rare disease. It cannot ethically be studied in human subjects under circumstances of intentional exposure. There are drugs with currently approved labeling by FDA for disease associated with *B. anthracis.* Labels for penicillin, tetracycline, doxycycline, and minocycline products list *B. anthracis* among the organisms susceptible to these agents. None of these agents is indicated specifically post-exposure for disease caused by inhaled *B. anthracis.*

Based on the *in vitro* activity of ciprofloxacin against this organism, the efficacy demonstrated in the prophylaxis of inhalational anthrax in Rhesus monkeys, and the concern about the possibility of the engineering of a strain that is resistant to penicillin and tetracycline, ciprofloxacin was recommended as a drug of choice for post-exposure prophylaxis by the CDC, Working Group for Civilian Biodefense (JAMA 1999;1735-45) and the 3rd Edition of the US Army Medical Research Institute of Infectious Diseases handbook "Medical Management of Biological Casualties."

The sponsor is submitting literature data to support this indication, including *in vitro* microbiology data and data from non-human primate (Rhesus monkey) models of infection. In addition, they have provided safety data gathered from previous use of ciprofloxacin in adults and pediatrics.

The proposed dosing recommendations are within the approved dosing range for adults. Although ciprofloxacin is not approved in pediatrics, there are safety data available from cystic fibrosis patients using daily doses of 30 mg/kg of ciprofloxacin. In addition, there are safety data on ciprofloxacin obtained through the FDA's Spontaneous Reporting System.

There are also long-term safety data in adults to cover the proposed duration of therapy for this indication. Two patient groups that received treatment with ciprofloxacin for > 30 days were identified (1) by literature search, and (2) by the sponsor's database pool. Data on the long-term safety in pediatrics are also included, but are limited to small numbers exposed.

II. INDICATION AND DOSAGES

Ciprofloxacin in tablet form was approved for human use in the US in 1987; the intravenous (IV) solutions were approved in 1990. Both are approved for a wide variety of indications. Dosing is specific to the approved indication, and ranges from 100-750 mg orally every 12 hours for the tablet. For the IV formulation, the approved dose ranges from 200 to 400 mg every 8 to 12 hours.

The proposed dosing regimens for ciprofloxacin for inhalational anthrax (post-exposure) are given below:

Patient Population	Oral dose	Intravenous dose
Adult	500 mg Q12h x 60 days	400 mg (not to exceed 800 mg) Q12h
Pediatric*	10-15 mg/kg (not to exceed 500 mg per dose) Q12h x 60 days	10-15 mg/kg Q12h (not to exceed 800 mg per day)

* For children greater than 45 kg, the adult dosage should be used

Therapy should be initiated immediately after suspected or confirmed exposure and continue for 60 days.

III. CLINICAL PHARMACOLOGY SYNOPSIS

What pharmacokinetic data are available from monkeys infected with inhalational anthrax?

The study of ciprofloxacin to prevent inhalational anthrax was performed in a non-human primate (macaque) model and is supported by *in vitro* data assessing the activity of ciprofloxacin against *B. anthracis*. The authors also measured peak and trough serum concentrations of ciprofloxacin after administration of doses calculated by extrapolation from human doses.

Kelly, et al. Serum Concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. Journal Infect Dis 1992;166:1184-7.

Note: The raw ciprofloxacin data from this study can be found in Appendix 1.

Male and female adult monkeys were studied with a mean body weight of 7.7 kg (range 5.1 to 13.0 kg), and a mean body surface area of 0.46 m^2 [redacted] This represents a mean of 26% of the 1.73 m^2 body surface area of a 65-kg, 170-cm human. Ten animals were exposed to aerosolized anthrax spores and received a single ciprofloxacin 250 mg dose per nasogastric tube (pngt) 24 hours following exposure, followed twelve hours later by ciprofloxacin 125 mg pngt every 12 hours for 30 days. Blood samples for measurement of peak ciprofloxacin concentrations were collected on Days 5, 9, 20, and 30. Trough concentrations were collected on Days 3, 5, 9, and 20.

None of 10 monkeys treated with ciprofloxacin died from anthrax within the 30-day treatment period. One monkey died on Day 5 from accidental injection of drug into the lung.

Figures 1 and 2 below present individual (mean ± SD) peak and trough blood levels of ciprofloxacin, respectively, for during the 30-day period of drug administration. The MIC_{90} of ciprofloxacin for *B. anthracis* is also presented.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

How does the exposure to ciprofloxacin in monkeys compare to humans?

Figures 3 and 4 (page 9) present individual (mean ± SD) serum or plasma concentrations of ciprofloxacin observed in the monkeys in the study performed by Kelly et al. compared with mean ± SD values obtained from the literature in a number of different human populations, including pediatrics. It should be noted that the pediatric data is derived from patients with cystic fibrosis (CF). It has been shown that the pharmacokinetics of ciprofloxacin in adult patients with CF are comparable to healthy adult subjects. Table 1 describes the populations and dosing regimens depicted in Figures 3 and 4.

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Table 5. Summary of Ciprofloxacin Pharmacokinetics from Various Literature Articles

Population	Dose/Regimen	Route	N	$C_{max,ss}$ (µg/mL) ± SD	$C_{min,ss}$ (µg/mL) ± SD	$AUC_{0-24,ss}$ (µg*h/mL) ± SD	Notes
Monkeys	250 mg x 1, then 125 mg po Q12h (*32 mg/kg x 1, then 16 mg/kg*)	PO	10	1.74 ± 1.41	0.17 ± 0.15	--	Loading dose of 2x used for 1st dose
Adults	500 mg Q12h (*7.1 mg/kg*)	PO	12	2.89 ± 0.54	0.28 ± 0.13	27.9 ± 5.72	At steady state
Adults	400 mg Q12h (*5.6 mg/kg*)	IV	--	4.56	0.2	25.4	At steady state
Human Males	400 mg x 1 (*5.6 mg/kg*)	IV	11	3.11 ± 0.61*	--	9.27 ± 1.51*	*Single dose, not at steady state
Obese Human Males	400 mg x 1 (*3.6 mg/kg*)	IV	17	2.66 ± 0.53*†	--	7.72 ± 1.49*	*Single dose, not at steady state
Peds, CF	10 mg/kg Q8h	IV	18	5.0 ± 1.5	0.39 ± 0.18	24.0 ± 6.4	Q8h dosing; different from proposed regimen
Peds, CF	20 mg/kg Q12h	PO	18	3.7 ± 1.4	0.42 ± 0.21	36.6 ± 12.0	Total dose 40 mg/kg; higher than proposed regimen
Peds, CF	10 mg/kg Q12h	IV	10	8.3	[redacted]	31.4	Similar to proposed regimen; levels obtained after 2nd IV dose (30 min infusion)
Peds, CF	15 mg/kg Q12h	PO	8	3.5	--	27.0	Similar to proposed regimen; levels obtained after 1st oral dose and preceded by two IV doses of 15 mg/kg over 30 min

CF- cystic fibrosis

†The C_{max} obtained after a single dose in obese human males is similar to that obtained after multiple dosing in adults of ideal body weight

Figure 3. Ciprofloxacin peak concentrations-animal and human studies

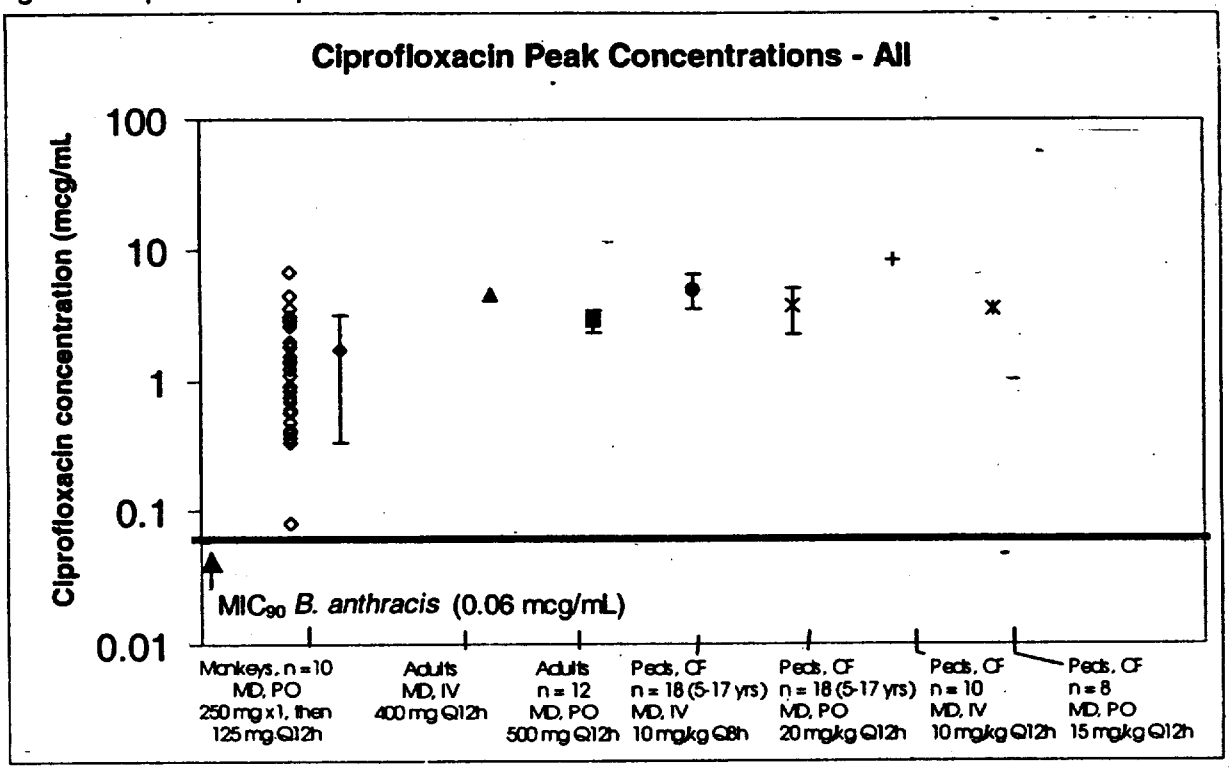
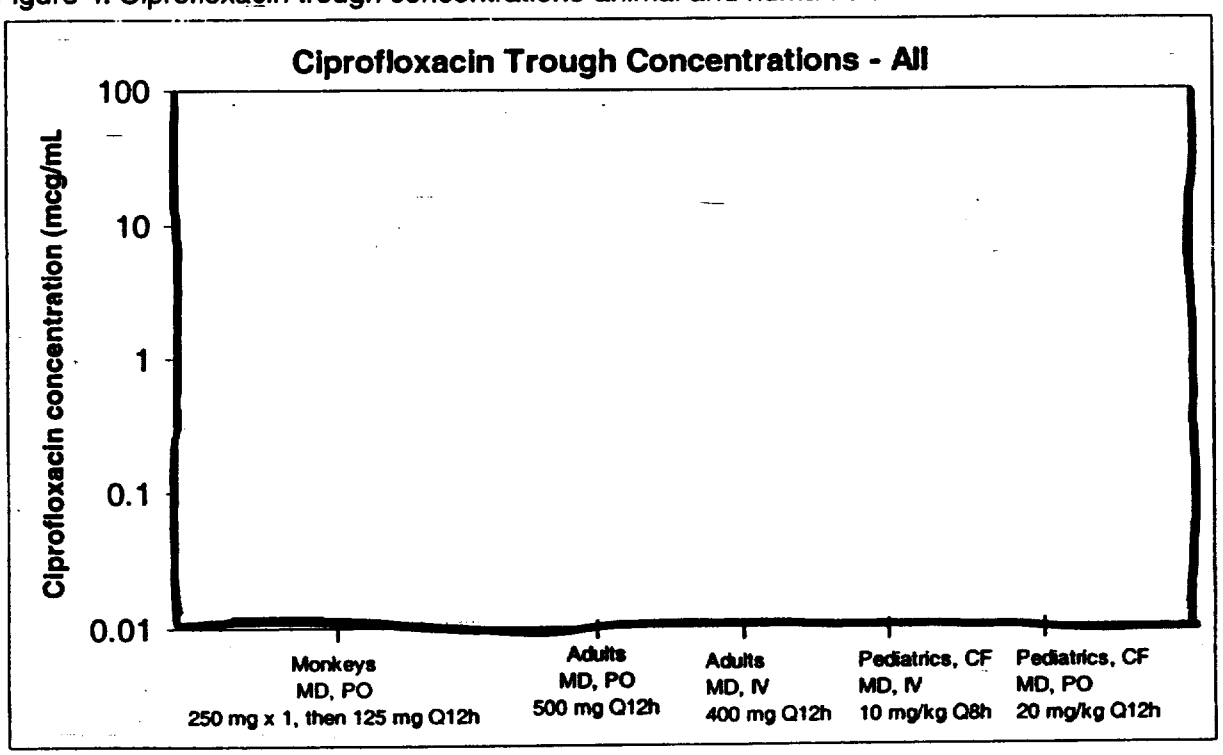


Figure 4. Ciprofloxacin trough concentrations-animal and human studies



Is there a pharmacokinetic/pharmacodynamic (PK/PD) relationship between ciprofloxacin exposure and efficacy in inhalational anthrax?

Fluoroquinolones, including ciprofloxacin, demonstrate concentration-dependent killing. The goal of a dosing regimen for these drugs is to maximize the serum concentrations. The peak concentration (C_{max})/MIC and/or AUC/MIC ratios are considered PK/PD parameters that best correlate with drug efficacy. Better correlation has been found with the AUC/MIC ratio than C_{max}/MIC, except possibly in infections where there is a significant risk of the emergence of resistant organisms. The relationship between these PK/PD parameters and drug efficacy has been demonstrated in animals models of infection as well as some clinical trials. Much of these data are derived from studies of infections with extracellular gram-negative organisms and in patients with nosocomial infections. Some recent data have demonstrated the usefulness of the AUC/MIC ratio for *Streptococcus pneumoniae.*

A comparison of pharmacokinetic with pharmacodynamic parameters in an animal model or human infection with inhalational anthrax cannot be made. *Bacillus anthracis* is gram-positive organism that exists intracellularly, so the optimal AUC/MIC or peak/MIC ratio is not known. In addition, there have been no prospective studies performed that link clinical outcome to drug exposure for this infection. However, in general when there is a demonstrated relationship between plasma concentrations of drug and response, pharmacokinetic data can be used as one way to characterize drug efficacy. Because of the unsuitability of performing a clinical trial in this particular infection, an alternative is to link the extent of ciprofloxacin systemic exposure in the animal model to what is seen in humans. As shown in Figures 3 and 4, the pharmacokinetics of ciprofloxacin in monkeys and humans are similar.

IV. GENERAL COMMENTS (NOT TO BE FORWARDED TO THE SPONSOR)

1. The sponsor has proposed a ciprofloxacin dose range of 10-15 mg/kg every 12 hours for pediatric patients treated with either IV or oral ciprofloxacin. In adults, a 500 mg oral dose given every 12 hours has been shown to produce an AUC equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 12 hours. In an ongoing study in pediatric patients with complicated urinary tract infections, ciprofloxacin is being initiated at a dose of 10 mg/kg IV every 12 hours, followed by 10-20 mg/kg orally every 12 hours.

   Therefore, the pediatric dosing recommendations for inhalational anthrax (post-exposure) will be modified, such that the IV dose will be 10 mg/kg infused over 60 minutes every 12 hours and the oral dose will be 15 mg/kg every 12 hours. Ciprofloxacin peak and trough concentrations obtained from pediatric patients administered this regimen, are consistent with what is seen in adults following 500 mg orally or 400 mg IV every 12 hours and are similar or in excess of the ciprofloxacin concentrations associated with survival in the monkey model.

V. LABELING RECOMMENDATIONS

1. [redacted]

1 page(s) of revised draft labeling has been redacted from this portion of the review.

VI. RECOMMENDATION

Based on what is known of the clinical pharmacology of ciprofloxacin, the clinical pharmacology/biopharmaceutics section of NDA 19-847/S-024 is acceptable and adequate to support approval.

/S/ 8/30/00

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) /S/ 8/30/00

OCPB Briefing July 27, 2000 (attendees): Arzu Selen and Funmi Ajayi

cc: HFD-590: /NDA 19-847; SLR-024
/PM/JensenV
/MOTL/RocaR
/MO/MeyerhoffA
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ
HFD-205: FOI

APPENDIX 1: Ciprofloxacin Pharmacokinetic Monkey Data (Kelly et al 1992)

Cipro Trough - Monkeys

Monkey ID	Day 3	Day 5	Day 9	Day 20
82A35	0.1	0.07	0.08	0.08
358D	0.22	0.1	0.1	0.23
B7388	0.1	0.1	0.08	0.12
T292	0.42	0.43		
410D	0.08	0.07	0.05	0.04
A32	0.18	0.22	0.16	0.06
45Y	0.13	0.1	0.26	0.05
84456A	0.18	0.21	0.16	0.1
T308	0.45	0.31	0.27	0.83
40B	0.2	0.07	0.08	0.08
RANGE: MIN				
MAX	0.45	0.43	0.27	0.83
GEOMEAN	0.18	0.14	0.12	0.11
MEAN	0.21	0.17	0.14	0.18
STDDEV	0.13	0.12	0.08	0.25

Cipro Peak - Monkeys

Monkey ID	Day 5	Day 9	Day 20	Day 30
82A35	0.91	0.56	0.39	0.39
358D	6.7	1.4	2.91	0.36
B7388	1.8	2.6	3.09	1.11
T292				
410D	0.08	2.6	3.57	1.8
A32	0.48	0.42	0.33	1.23
45Y	0.84	1.56	0.75	2.94
84456A	0.39	0.69	1.41	0.6
T308	1.98	2.91	4.47	1.56
40B	3.12	1.38	2.58	2.82
RANGE: MIN				
MAX	6.7	2.91	4.47	2.94
GEOMEAN	0.98	1.29	1.55	1.12
MEAN	1.81	1.57	2.17	1.42
STDDEV	2.07	0.94	1.50	0.96

Reviewer's Comment: The mean ciprofloxacin concentrations achieved following dosing to steady state (expected C_{max} and trough) expressed in the label are based on a calculation of the geomentric mean as performed by the investigators (Kelly et al 1992). The numbers above were obtained from the raw data sheets and are slightly different due to difficulties in deciphering the numbers.

Steady State Parameters	*Geometric Mean Values (µg/mL)*	
	Kelly et al	*Reviewer's Analysis*
Expected C_{max}	*0.98 – 1.69*	*0.98 – 1.55*
Trough	*0.12 – 0.19*	*0.11 – 0.18*

APPENDIX 2: Literature Reference List

1. Gonzales MA, Uribe F, Moisen SD, et al. Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother 1984;26:741-4.

2. Peltola H, Ukkonen P, Saxen H, et al. Single-dose and steady-state pharmacokinetics of a new oral suspension of ciprofloxacin in children. Pediatrics 1998;101:658-62.

3. Rubio TT, Miles MV, Lettieri JT, et al. Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbation. Pediatr Infect Dise J 1997;16:112-7.

4. Schaefer HG, Stass H, Wedgwood J, et al. Pharmacokinetics of ciprofloxacin in pediatric cystic fibrosis patients. Antimicrob Agents Chemother 1996;40:29-34.

5. Peltola H, Vaarala M, Renkonen OV, et al. Pharmacokinetics of single-dose oral ciprofloxacin in infants and small children. Antimicrob Agents Chemother 1992;36:1086-90.

6. Schaad UB, Salam MA, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr Infect Dis J 1995;14:1-9.

7. Allard S, Kinzig M, Boivin G, et al. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Thery 1993;54:368-73.

8. Neuman M. Clinical pharmacokinetics of the newer antibacterial 4-quinolones. Clin Pharmacokinet 1988;14:96-121.

9. Davis RL, Koup JR, Williams-Warren J, et al. Pharmacokinetics of ciprofloxacin in cystic fibrosis. Antimicrob Agents Chemother 1987;31:915-9.

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CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	19-858/S-021
Submission Date:	2/29/00
Drug:	Ciprofloxacin (Cipro®) IV in 0.9% Saline
Sponsor:	Bayer Corporation West Haven, CT
Type of Submission:	Efficacy supplement for the addition of the indication of inhalational anthrax (post-exposure)
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

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I. BACKGROUND

Anthrax is a bacterial infection, caused by a gram-positive rod, which has been recognized as a human pathogen causing cutaneous, gastrointestinal, and inhalational disease. These forms of infection with *Bacillus anthracis* have been traditionally associated with agricultural or industrial exposures. Today, human anthrax is rare in the United States though it remains an endemic disease in other areas of the world. Most recently, attention has turned to *B. anthracis* as a possible agent of biological warfare or bioterrorism.

The Bayer Corporation, responding to an expressed public health need, has submitted an application for the addition of the indication inhalational anthrax (post-exposure) to the label of Cipro® (ciprofloxacin). This is the first antimicrobial drug application submitted to the Food and Drug Administration (FDA) for an indication resulting from the intentional use of a biological agent. The approval of this indication will be based on the use of a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, under the accelerated approval regulations (21 CFR 314.510 subpart H).

Inhalational anthrax is an extremely rare disease. It cannot ethically be studied in human subjects under circumstances of intentional exposure. There are drugs with currently approved labeling by FDA for disease associated with *B. anthracis*. Labels for penicillin, tetracycline, doxycycline, and minocycline products list *B. anthracis* among the organisms susceptible to these agents. None of these agents is indicated specifically post-exposure for disease caused by inhaled *B. anthracis*.

Based on the *in vitro* activity of ciprofloxacin against this organism, the efficacy demonstrated in the prophylaxis of inhalational anthrax in Rhesus monkeys, and the concern about the possibility of the engineering of a strain that is resistant to penicillin and tetracycline, ciprofloxacin was recommended as a drug of choice for post-exposure prophylaxis by the CDC, Working Group for Civilian Biodefense (JAMA 1999;1735-45) and the 3rd Edition of the US Army Medical Research Institute of Infectious Diseases handbook "Medical Management of Biological Casualties."

The sponsor is submitting literature data to support this indication, including *in vitro* microbiology data and data from non-human primate (Rhesus monkey) models of infection. In addition, they have provided safety data gathered from previous use of ciprofloxacin in adults and pediatrics.

The proposed dosing recommendations are within the approved dosing range for adults. Although ciprofloxacin is not approved in pediatrics, there are safety data available from cystic fibrosis patients using daily doses of 30 mg/kg of ciprofloxacin. In addition, there are safety data on ciprofloxacin obtained through the FDA's Spontaneous Reporting System.

There are also long-term safety data in adults to cover the proposed duration of therapy for this indication. Two patient groups that received treatment with ciprofloxacin for > 30 days were identified (1) by literature search, and (2) by the sponsor's database pool. Data on the long-term safety in pediatrics are also included, but are limited to small numbers exposed.

II. INDICATION AND DOSAGES

Ciprofloxacin in tablet form was approved for human use in the US in 1987; the intravenous (IV) solutions were approved in 1990. Both are approved for a wide variety of indications. Dosing is specific to the approved indication, and ranges from 100-750 mg orally every 12 hours for the tablet. For the IV formulation, the approved dose ranges from 200 to 400 mg every 8 to 12 hours.

The proposed dosing regimens for ciprofloxacin for inhalational anthrax (post-exposure) are given below:

Patient Population	Oral dose	Intravenous dose
Adult	500 mg Q12h x 60 days	400 mg (not to exceed 800 mg) Q12h
Pediatric*	10-15 mg/kg (not to exceed 500 mg per dose) Q12h x 60 days	10-15 mg/kg Q12h (not to exceed 800 mg per day)

* For children greater than 45 kg, the adult dosage should be used

Therapy should be initiated immediately after suspected or confirmed exposure and continue for 60 days.

III. CLINICAL PHARMACOLOGY SYNOPSIS

What pharmacokinetic data are available from monkeys infected with inhalational anthrax?

The study of ciprofloxacin to prevent inhalational anthrax was performed in a non-human primate (macaque) model and is supported by *in vitro* data assessing the activity of ciprofloxacin against *B. anthracis*. The authors also measured peak and trough serum concentrations of ciprofloxacin after administration of doses calculated by extrapolation from human doses.

Kelly, et al. Serum Concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. Journal Infect Dis 1992;166:1184-7.

Note: The raw ciprofloxacin data from this study can be found in Appendix 1.

Male and female adult monkeys were studied with a mean body weight of 7.7 kg (range 5.1 to 13.0 kg), and a mean body surface area of 0.46 m^2 [redacted] This represents a mean of 26% of the 1.73 m^2 body surface area of a 65-kg, 170-cm human. Ten animals were exposed to aerosolized anthrax spores and received a single ciprofloxacin 250 mg dose per nasogastric tube (pngt) 24 hours following exposure, followed twelve hours later by ciprofloxacin 125 mg pngt every 12 hours for 30 days. Blood samples for measurement of peak ciprofloxacin concentrations were collected on Days 5, 9, 20, and 30. Trough concentrations were collected on Days 3, 5, 9, and 20.

None of 10 monkeys treated with ciprofloxacin died from anthrax within the 30-day treatment period. One monkey died on Day 5 from accidental injection of drug into the lung.

Figures 1 and 2 below present individual (mean ± SD) peak and trough blood levels of ciprofloxacin, respectively, for during the 30-day period of drug administration. The MIC_{90} of ciprofloxacin for *B. anthracis* is also presented.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

How does the exposure to ciprofloxacin in monkeys compare to humans?

Figures 3 and 4 (page 9) present individual (mean ± SD) serum or plasma concentrations of ciprofloxacin observed in the monkeys in the study performed by Kelly et al. compared with mean ± SD values obtained from the literature in a number of different human populations, including pediatrics. It should be noted that the pediatric data is derived from patients with cystic fibrosis (CF). It has been shown that the pharmacokinetics of ciprofloxacin in adult patients with CF are comparable to healthy adult subjects. Table 1 describes the populations and dosing regimens depicted in Figures 3 and 4.

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Table 5. Summary of Ciprofloxacin Pharmacokinetics from Various Literature Articles

Population	Dose/Regimen	Route	N	$C_{max,ss}$ (μg/mL) ± SD	$C_{min,ss}$ (μg/mL) ± SD	$AUC_{0-24,ss}$ (μg*h/mL) ± SD	Notes
Monkeys	250 mg x 1, then 125 mg po Q12h (*32 mg/kg x 1, then 16 mg/kg*)	PO	10	1.74 ± 1.41	0.17 ± 0.15	--	Loading dose of 2x used for 1st dose
Adults	500 mg Q12h (*7.1 mg/kg*)	PO	12	2.89 ± 0.54	0.28 ± 0.13	27.9 ± 5.72	At steady state
Adults	400 mg Q12h (*5.6 mg/kg*)	IV	--	4.56	0.2	25.4	At steady state
Human Males	400 mg x 1 (*5.6 mg/kg*)	IV	11	3.11 ± 0.61*	--	9.27 ± 1.51*	*Single dose, not at steady state
Obese Human Males	400 mg x 1 (*3.6 mg/kg*)	IV	17	2.66 ± 0.53*†	--	7.72 ± 1.49*	*Single dose, not at steady state
Peds, CF	10 mg/kg Q8h	IV	18	5.0 ± 1.5	0.39 ± 0.18	24.0 ± 6.4	Q8h dosing; different from proposed regimen
Peds, CF	20 mg/kg Q12h	PO	18	3.7 ± 1.4	0.42 ± 0.21	36.6 ± 12.0	Total dose 40 mg/kg; higher than proposed regimen
Peds, CF	10 mg/kg Q12h	IV	10	8.3	[redacted]	31.4	Similar to proposed regimen; levels obtained after 2nd IV dose (30 min infusion)
Peds, CF	15 mg/kg Q12h	PO	8	3.5	--	27.0	Similar to proposed regimen; levels obtained after 1st oral dose and preceded by two IV doses of 15 mg/kg over 30 min

CF- cystic fibrosis

†The C_{max} obtained after a single dose in obese human males is similar to that obtained after multiple dosing in adults of ideal body weight

Figure 3. Ciprofloxacin peak concentrations-animal and human studies

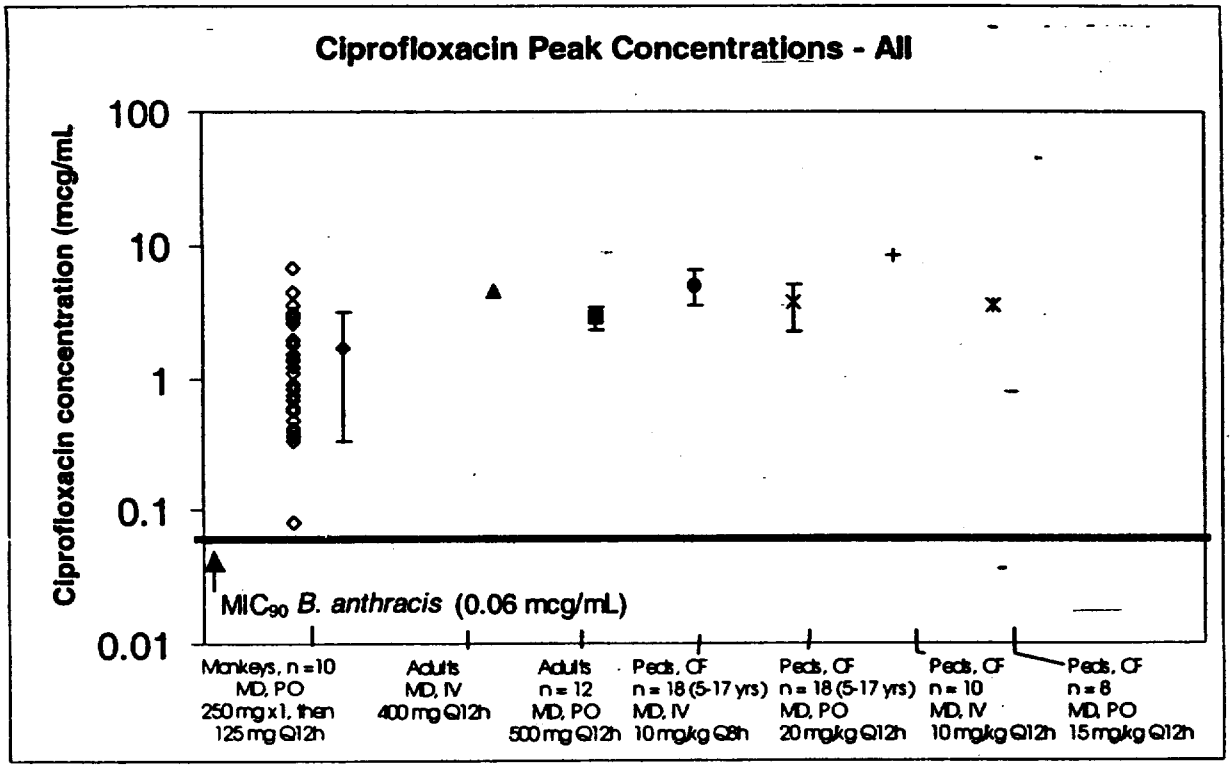
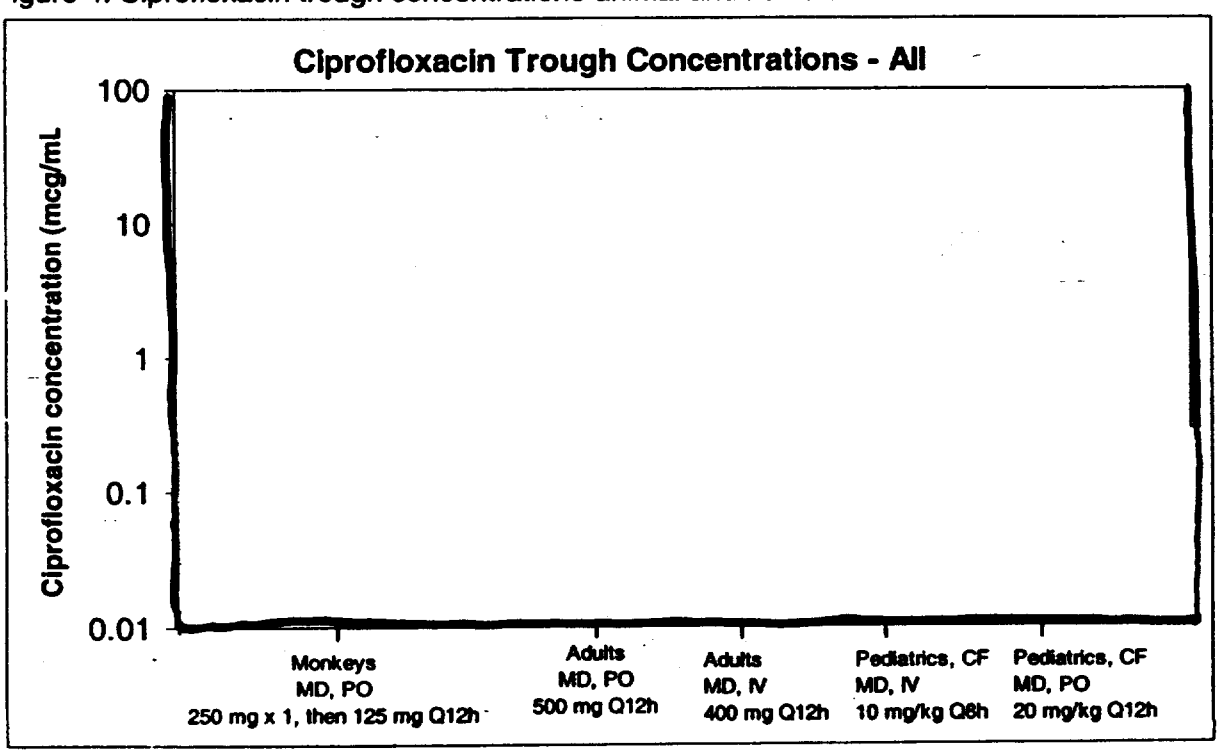


Figure 4. Ciprofloxacin trough concentrations-animal and human studies



Is there a pharmacokinetic/pharmacodynamic (PK/PD) relationship between ciprofloxacin exposure and efficacy in inhalational anthrax?

Fluoroquinolones, including ciprofloxacin, demonstrate concentration-dependent killing. The goal of a dosing regimen for these drugs is to maximize the serum concentrations. The peak concentration (C_{max})/MIC and/or AUC/MIC ratios are considered PK/PD parameters that best correlate with drug efficacy. Better correlation has been found with the AUC/MIC ratio than C_{max}/MIC, except possibly in infections where there is a significant risk of the emergence of resistant organisms. The relationship between these PK/PD parameters and drug efficacy has been demonstrated in animals models of infection as well as some clinical trials. Much of these data are derived from studies of infections with extracellular gram-negative organisms and in patients with nosocomial infections. Some recent data have demonstrated the usefulness of the AUC/MIC ratio for *Streptococcus pneumoniae.*

A comparison of pharmacokinetic with pharmacodynamic parameters in an animal model or human infection with inhalational anthrax cannot be made. *Bacillus anthracis* is gram-positive organism that exists intracellularly, so the optimal AUC/MIC or peak/MIC ratio is not known. In addition, there have been no prospective studies performed that link clinical outcome to drug exposure for this infection. However, in general when there is a demonstrated relationship between plasma concentrations of drug and response, pharmacokinetic data can be used as one way to characterize drug efficacy. Because of the unsuitability of performing a clinical trial in this particular infection, an alternative is to link the extent of ciprofloxacin systemic exposure in the animal model to what is seen in humans. As shown in Figures 3 and 4, the pharmacokinetics of ciprofloxacin in monkeys and humans are similar.

IV. GENERAL COMMENTS (NOT TO BE FORWARDED TO THE SPONSOR)

1. The sponsor has proposed a ciprofloxacin dose range of 10-15 mg/kg every 12 hours for pediatric patients treated with either IV or oral ciprofloxacin. In adults, a 500 mg oral dose given every 12 hours has been shown to produce an AUC equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 12 hours. In an ongoing study in pediatric patients with complicated urinary tract infections, ciprofloxacin is being initiated at a dose of 10 mg/kg IV every 12 hours, followed by 10-20 mg/kg orally every 12 hours.

   Therefore, the pediatric dosing recommendations for inhalational anthrax (post-exposure) will be modified, such that the IV dose will be 10 mg/kg infused over 60 minutes every 12 hours and the oral dose will be 15 mg/kg every 12 hours. Ciprofloxacin peak and trough concentrations obtained from pediatric patients administered this regimen, are consistent with what is seen in adults following 500 mg orally or 400 mg IV every 12 hours and are similar or in excess of the ciprofloxacin concentrations associated with survival in the monkey model.

V. LABELING RECOMMENDATIONS

1 page(s) of revised draft labeling has been redacted from this portion of the review.

VI. RECOMMENDATION

Based on what is known of the clinical pharmacology of ciprofloxacin, the clinical pharmacology/biopharmaceutics section of NDA 19-858/S-021 is acceptable and adequate to support approval.

/S/ 8/30/00

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) /S/ 8/30/00

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APPENDIX 1: Ciprofloxacin Pharmacokinetic Monkey Data (Kelly et al 1992)

Cipro Trough - Monkeys

Monkey ID	Day 3	Day 5	Day 9	Day 20
82A35	0.1	0.07	0.08	0.08
358D	0.22	0.1	0.1	0.23
B7388	0.1	0.1	0.08	0.12
T292	0.42	0.43		
410D	0.08	0.07	0.05	0.04
A32	0.18	0.22	0.16	0.06
45Y	0.13	0.1	0.26	0.05
84456A	0.18	0.21	0.16	0.1
T308	0.45	0.31	0.27	0.83
40B	0.2	0.07	0.08	0.08
RANGE MIN				
MAX	0.45	0.43	0.27	0.83
GEOMEAN	0.18	0.14	0.12	0.11
MEAN	0.21	0.17	0.14	0.18
STDDEV	0.13	0.12	0.08	0.25

Cipro Peak - Monkeys

Monkey ID	Day 5	Day 9	Day 20	Day 30
82A35	0.91	0.56	0.39	0.39
358D	6.7	1.4	2.91	0.36
B7388	1.8	2.6	3.09	1.11
T292				
410D	0.08	2.6	3.57	1.8
A32	0.48	0.42	0.33	1.23
45Y	0.84	1.56	0.75	2.94
84456A	0.39	0.69	1.41	0.6
T308	1.98	2.91	4.47	1.56
40B	3.12	1.38	2.58	2.82
RANGE MIN				
MAX	6.7	2.91	3.47	2.94
GEOMEAN	0.98	1.29	1.55	1.12
MEAN	1.81	1.57	2.17	1.42
STDDEV	2.07	0.94	1.50	0.96

Reviewer's Comment: The mean ciprofloxacin concentrations achieved following dosing to steady state (expected C_{max} and trough) expressed in the label are based on a calculation of the geomentric mean as performed by the investigators (Kelly et al 1992). The numbers above were obtained from the raw data sheets and are slightly different due to difficulties in deciphering the numbers.

Steady State Parameters	*Geometric Mean Values (µg/mL)*	
	Kelly et al	*Reviewer's Analysis*
Expected C_{max}	*0.98 – 1.69*	*0.98 – 1.55*
Trough	*0.12 – 0.19*	*0.11 – 0.18*

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CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	19-857/S-027
Submission Date:	2/29/00
Drug:	Ciprofloxacin (Cipro®) IV in 5% Dextrose
Sponsor:	Bayer Corporation West Haven, CT
Type of Submission:	Efficacy supplement for the addition of the indication of inhalational anthrax (post-exposure)
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

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I. BACKGROUND

Anthrax is a bacterial infection, caused by a gram-positive rod, which has been recognized as a human pathogen causing cutaneous, gastrointestinal, and inhalational disease. These forms of infection with *Bacillus anthracis* have been traditionally associated with agricultural or industrial exposures. Today, human anthrax is rare in the United States though it remains an endemic disease in other areas of the world. Most recently, attention has turned to *B. anthracis* as a possible agent of biological warfare or bioterrorism.

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Based on the *in vitro* activity of ciprofloxacin against this organism, the efficacy demonstrated in the prophylaxis of inhalational anthrax in Rhesus monkeys, and the concern about the possibility of the engineering of a strain that is resistant to penicillin and tetracycline, ciprofloxacin was recommended as a drug of choice for post-exposure prophylaxis by the CDC, Working Group for Civilian Biodefense (JAMA 1999;1735-45) and the 3rd Edition of the US Army Medical Research Institute of Infectious Diseases handbook "Medical Management of Biological Casualties."

The sponsor is submitting literature data to support this indication, including *in vitro* microbiology data and data from non-human primate (Rhesus monkey) models of infection. In addition, they have provided safety data gathered from previous use of ciprofloxacin in adults and pediatrics.

The proposed dosing recommendations are within the approved dosing range for adults. Although ciprofloxacin is not approved in pediatrics, there are safety data available from cystic fibrosis patients using daily doses of 30 mg/kg of ciprofloxacin. In addition, there are safety data on ciprofloxacin obtained through the FDA's Spontaneous Reporting System.

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II. INDICATION AND DOSAGES

Ciprofloxacin in tablet form was approved for human use in the US in 1987; the intravenous (IV) solutions were approved in 1990. Both are approved for a wide variety of indications. Dosing is specific to the approved indication, and ranges from 100-750 mg orally every 12 hours for the tablet. For the IV formulation, the approved dose ranges from 200 to 400 mg every 8 to 12 hours.

The proposed dosing regimens for ciprofloxacin for inhalational anthrax (post-exposure) are given below:

Patient Population	Oral dose	Intravenous dose
Adult	500 mg Q12h x 60 days	400 mg (not to exceed 800 mg) Q12h
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* For children greater than 45 kg, the adult dosage should be used

Therapy should be initiated immediately after suspected or confirmed exposure and continue for 60 days.

III. CLINICAL PHARMACOLOGY SYNOPSIS

What pharmacokinetic data are available from monkeys infected with inhalational anthrax?

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Kelly, et al. Serum Concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. Journal Infect Dis 1992;166:1184-7.

Note: The raw ciprofloxacin data from this study can be found in Appendix 1.

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None of 10 monkeys treated with ciprofloxacin died from anthrax within the 30-day treatment period. One monkey died on Day 5 from accidental injection of drug into the lung.

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Table 5. Summary of Ciprofloxacin Pharmacokinetics from Various Literature Articles

Population	Dose/Regimen	Route	N	$C_{max,ss}$ (µg/mL) ± SD	$C_{min,ss}$ (µg/mL) ± SD	$AUC_{0-24,ss}$ (µg*h/mL) ± SD	Notes
Monkeys	250 mg x 1, then 125 mg po Q12h (*32 mg/kg x 1, then 16 mg/kg*)	PO	10	1.74 ± 1.41	0.17 ± 0.15	--	Loading dose of 2x used for 1st dose
Adults	500 mg Q12h (*7.1 mg/kg*)	PO	12	2.89 ± 0.54	0.28 ± 0.13	27.9 ± 5.72	At steady state
Adults	400 mg Q12h (*5.6 mg/kg*)	IV	--	4.56	0.2	25.4	At steady state
Human Males	400 mg x 1 (*5.6 mg/kg*)	IV	11	3.11 ± 0.61*	--	9.27 ± 1.51*	*Single dose, not at steady state
Obese Human Males	400 mg x 1 (*3.6 mg/kg*)	IV	17	2.66 ± 0.53*†	--	7.72 ± 1.49*	*Single dose, not at steady state
Peds, CF	10 mg/kg Q8h	IV	18	5.0 ± 1.5	0.39 ± 0.18	24.0 ± 6.4	Q8h dosing; different from proposed regimen
Peds, CF	20 mg/kg Q12h	PO	18	3.7 ± 1.4	0.42 ± 0.21	36.6 ± 12.0	Total dose 40 mg/kg; higher than proposed regimen
Peds, CF	10 mg/kg Q12h	IV	10	8.3	[redacted]	31.4	Similar to proposed regimen; levels obtained after 2nd IV dose (30 min infusion)
Peds, CF	15 mg/kg Q12h	PO	8	3.5	--	27.0	Similar to proposed regimen; levels obtained after 1st oral dose and preceded by two IV doses of 15 mg/kg over 30 min

CF- cystic fibrosis

†The C_{max} obtained after a single dose in obese human males is similar to that obtained after multiple dosing in adults of ideal body weight

Figure 3. Ciprofloxacin peak concentrations-animal and human studies

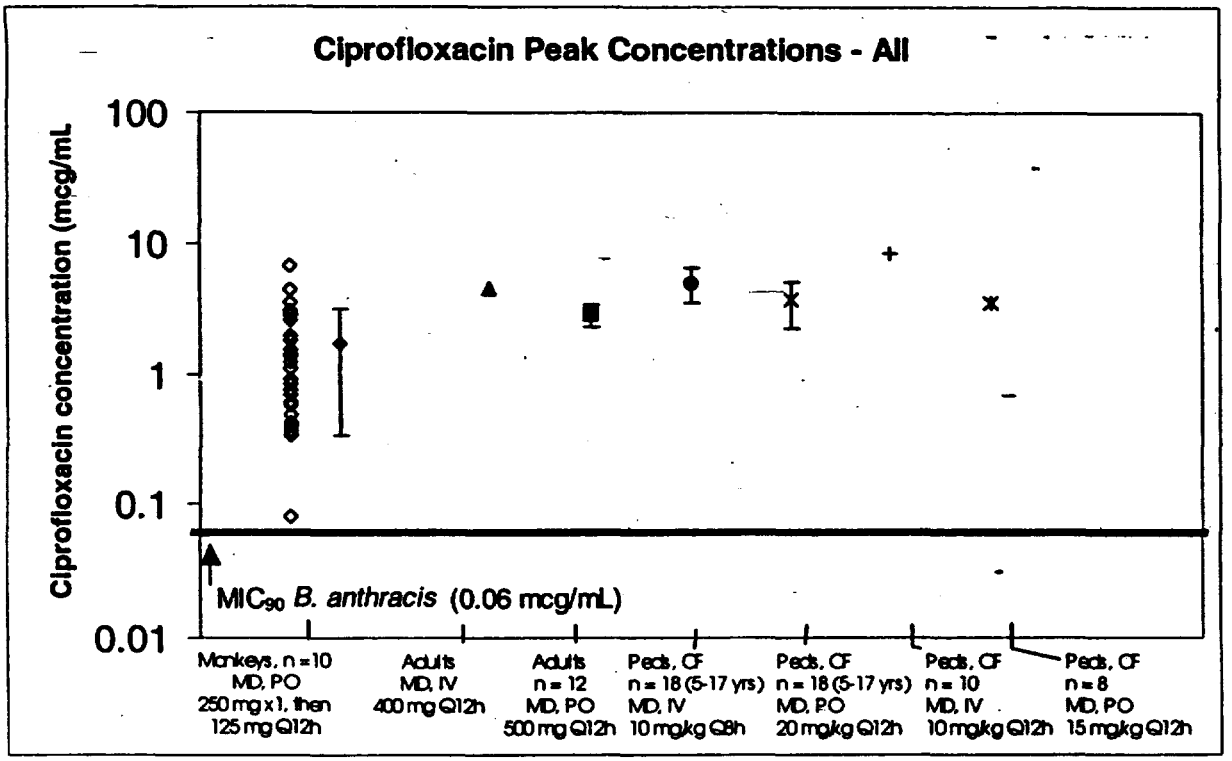
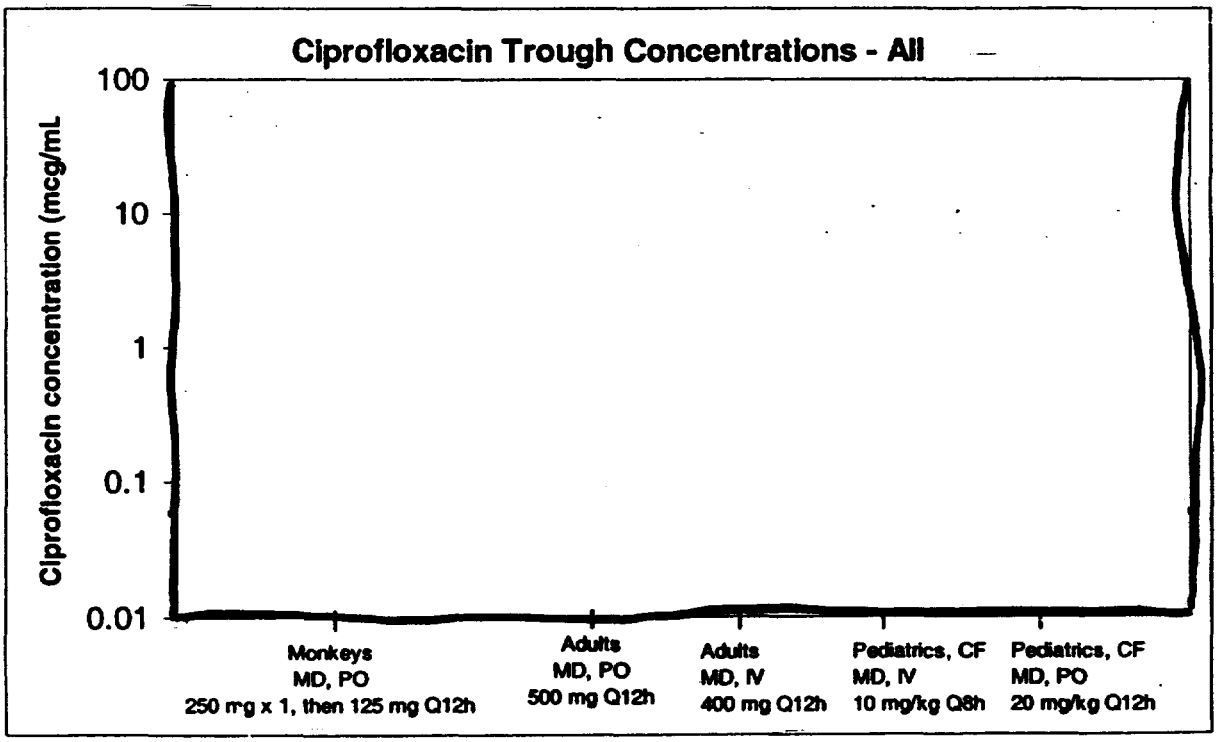


Figure 4. Ciprofloxacin trough concentrations-animal and human studies



Is there a pharmacokinetic/pharmacodynamic (PK/PD) relationship between ciprofloxacin exposure and efficacy in inhalational anthrax?

Fluoroquinolones, including ciprofloxacin, demonstrate concentration-dependent killing. The goal of a dosing regimen for these drugs is to maximize the serum concentrations. The peak concentration (C_{max})/MIC and/or AUC/MIC ratios are considered PK/PD parameters that best correlate with drug efficacy. Better correlation has been found with the AUC/MIC ratio than C_{max}/MIC, except possibly in infections where there is a significant risk of the emergence of resistant organisms. The relationship between these PK/PD parameters and drug efficacy has been demonstrated in animals models of infection as well as some clinical trials. Much of these data are derived from studies of infections with extracellular gram-negative organisms and in patients with nosocomial infections. Some recent data have demonstrated the usefulness of the AUC/MIC ratio for *Streptococcus pneumoniae.*

A comparison of pharmacokinetic with pharmacodynamic parameters in an animal model or human infection with inhalational anthrax cannot be made. *Bacillus anthracis* is gram-positive organism that exists intracellularly, so the optimal AUC/MIC or peak/MIC ratio is not known. In addition, there have been no prospective studies performed that link clinical outcome to drug exposure for this infection. However, in general when there is a demonstrated relationship between plasma concentrations of drug and response, pharmacokinetic data can be used as one way to characterize drug efficacy. Because of the unsuitability of performing a clinical trial in this particular infection, an alternative is to link the extent of ciprofloxacin systemic exposure in the animal model to what is seen in humans. As shown in Figures 3 and 4, the pharmacokinetics of ciprofloxacin in monkeys and humans are similar.

IV. GENERAL COMMENTS (NOT TO BE FORWARDED TO THE SPONSOR)

1. The sponsor has proposed a ciprofloxacin dose range of 10-15 mg/kg every 12 hours for pediatric patients treated with either IV or oral ciprofloxacin. In adults, a 500 mg oral dose given every 12 hours has been shown to produce an AUC equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 12 hours. In an ongoing study in pediatric patients with complicated urinary tract infections, ciprofloxacin is being initiated at a dose of 10 mg/kg IV every 12 hours, followed by 10-20 mg/kg orally every 12 hours.

   Therefore, the pediatric dosing recommendations for inhalational anthrax (post-exposure) will be modified, such that the IV dose will be 10 mg/kg infused over 60 minutes every 12 hours and the oral dose will be 15 mg/kg every 12 hours. Ciprofloxacin peak and trough concentrations obtained from pediatric patients administered this regimen, are consistent with what is seen in adults following 500 mg orally or 400 mg IV every 12 hours and are similar or in excess of the ciprofloxacin concentrations associated with survival in the monkey model.

V. LABELING RECOMMENDATIONS

1. [redacted]

1 page(s) of revised draft labeling has been redacted from this portion of the review.

VI. RECOMMENDATION

Based on what is known of the clinical pharmacology of ciprofloxacin, the clinical pharmacology/biopharmaceutics section of NDA 19-857/S-027 is acceptable and adequate to support approval.

/S/ 8/30/00

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) /S/ 8/30/00

OCPB Briefing July 27, 2000 (attendees): Arzu Selen and Funmi Ajayi

cc: HFD-590: /NDA 19-857; SLR-027
/PM/JensenV
/MOTL/RocaR
/MO/MeyerhoffA
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ
HFD-205: FOI

APPENDIX 1: Ciprofloxacin Pharmacokinetic Monkey Data (Kelly et al 1992)

Cipro Trough - Monkeys

Monkey ID	Day 3	Day 5	Day 9	Day 20
82A35	0.1	0.07	0.08	0.08
358D	0.22	0.1	0.1	0.23
B7388	0.1	0.1	0.08	0.12
T292	0.42	0.43		
410D	0.08	0.07	0.05	0.04
A32	0.18	0.22	0.16	0.06
45Y	0.13	0.1	0.26	0.05
84456A	0.18	0.21	0.16	0.1
T308	0.45	0.31	0.27	0.83
40B	0.2	0.07	0.08	0.08
RANGE MIN				
MAX	0.45	0.43	0.27	0.83
GEOMEAN	0.18	0.14	0.12	0.11
MEAN	0.21	0.17	0.14	0.18
STDDEV	0.13	0.12	0.08	0.25

Cipro Peak - Monkeys

Monkey ID	Day 5	Day 9	Day 20	Day 30
82A35	0.91	0.56	0.39	0.39
358D	6.7	1.4	2.91	0.36
B7388	1.8	2.6	3.09	1.11
T292				
410D	0.08	2.6	3.57	1.8
A32	0.48	0.42	0.33	1.23
45Y	0.84	1.56	0.75	2.94
84456A	0.39	0.69	1.41	0.6
T308	1.98	2.91	4.47	1.56
40B	3.12	1.38	2.58	2.82
RANGE MIN				
MAX	6.7	2.91	4.47	2.94
GEOMEAN	0.98	1.29	1.55	1.12
MEAN	1.81	1.57	2.17	1.42
STDDEV	2.07	0.94	1.50	0.96

Reviewer's Comment: The mean ciprofloxacin concentrations achieved following dosing to steady state (expected C_{max} and trough) expressed in the label are based on a calculation of the geomentric mean as performed by the investigators (Kelly et al 1992). The numbers above were obtained from the raw data sheets and are slightly different due to difficulties in deciphering the numbers.

Steady State Parameters	*Geometric Mean Values (µg/mL)*	
	Kelly et al	*Reviewer's Analysis*
Expected C_{max}	*0.98 – 1.69*	*0.98 – 1.55*
Trough	*0.12 – 0.19*	*0.11 – 0.18*

APPENDIX 2: Literature Reference List

1. Gonzales MA, Uribe F, Moisen SD, et al. Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother 1984;26:741-4.

2. Peltola H, Ukkonen P, Saxen H, et al. Single-dose and steady-state pharmacokinetics of a new oral suspension of ciprofloxacin in children. Pediatrics 1998;101:658-62.

3. Rubio TT, Miles MV, Lettieri JT, et al. Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbation. Pediatr Infect Dise J 1997;16:112-7.

4. Schaefer HG, Stass H, Wedgwood J, et al. Pharmacokinetics of ciprofloxacin in pediatric cystic fibrosis patients. Antimicrob Agents Chemother 1996;40:29-34.

5. Peltola H, Vaarala M, Renkonen OV, et al. Pharmacokinetics of single-dose oral ciprofloxacin in infants and small children. Antimicrob Agents Chemother 1992;36:1086-90.

6. Schaad UB, Salam MA, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr Infect Dis J 1995;14:1-9.

7. Allard S, Kinzig M, Boivin G, et al. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Thery 1993;54:368-73.

8. Neuman M. Clinical pharmacokinetics of the newer antibacterial 4-quinolones. Clin Pharmacokinet 1988;14:96-121.

9. Davis RL, Koup JR, Williams-Warren J, et al. Pharmacokinetics of ciprofloxacin in cystic fibrosis. Antimicrob Agents Chemother 1987;31:915-9.

10. Reed MD, Stern RC, Myers CM, et al. Lack of unique ciprofloxacin pharmacokinetic characteristics in patients with cystic fibrosis. J Clin Pharmacol 1988;28:691-9.

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	20-780/S-008
Submission Date:	2/29/00
Drug:	Ciprofloxacin (Cipro®) Oral Suspension
Sponsor:	Bayer Corporation West Haven, CT
Type of Submission:	Efficacy supplement for the addition of the indication of inhalational anthrax (post-exposure)
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

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I. BACKGROUND

Anthrax is a bacterial infection, caused by a gram-positive rod, which has been recognized as a human pathogen causing cutaneous, gastrointestinal, and inhalational disease. These forms of infection with *Bacillus anthracis* have been traditionally associated with agricultural or industrial exposures. Today, human anthrax is rare in the United States though it remains an endemic disease in other areas of the world. Most recently, attention has turned to *B. anthracis* as a possible agent of biological warfare or bioterrorism.

The Bayer Corporation, responding to an expressed public health need, has submitted an application for the addition of the indication inhalational anthrax (post-exposure) to the label of Cipro® (ciprofloxacin). This is the first antimicrobial drug application submitted to the Food and Drug Administration (FDA) for an indication resulting from the intentional use of a biological agent. The approval of this indication will be based on the use of a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, under the accelerated approval regulations (21 CFR 314.510 subpart H).

Inhalational anthrax is an extremely rare disease. It cannot ethically be studied in human subjects under circumstances of intentional exposure. There are drugs with currently approved labeling by FDA for disease associated with *B. anthracis*. Labels for penicillin, tetracycline, doxycycline, and minocycline products list *B. anthracis* among the organisms susceptible to these agents. None of these agents is indicated specifically post-exposure for disease caused by inhaled *B. anthracis*.

Based on the *in vitro* activity of ciprofloxacin against this organism, the efficacy demonstrated in the prophylaxis of inhalational anthrax in Rhesus monkeys, and the concern about the possibility of the engineering of a strain that is resistant to penicillin and tetracycline, ciprofloxacin was recommended as a drug of choice for post-exposure prophylaxis by the CDC, Working Group for Civilian Biodefense (JAMA 1999;1735-45) and the 3rd Edition of the US Army Medical Research Institute of Infectious Diseases handbook "Medical Management of Biological Casualties."

The sponsor is submitting literature data to support this indication, including *in vitro* microbiology data and data from non-human primate (Rhesus monkey) models of infection. In addition, they have provided safety data gathered from previous use of ciprofloxacin in adults and pediatrics.

The proposed dosing recommendations are within the approved dosing range for adults. Although ciprofloxacin is not approved in pediatrics, there are safety data available from cystic fibrosis patients using daily doses of 30 mg/kg of ciprofloxacin. In addition, there are safety data on ciprofloxacin obtained through the FDA's Spontaneous Reporting System.

There are also long-term safety data in adults to cover the proposed duration of therapy for this indication. Two patient groups that received treatment with ciprofloxacin for > 30 days were identified (1) by literature search, and (2) by the sponsor's database pool. Data on the long-term safety in pediatrics are also included, but are limited to small numbers exposed.

II. INDICATION AND DOSAGES

Ciprofloxacin in tablet form was approved for human use in the US in 1987; the intravenous (IV) solutions were approved in 1990. Both are approved for a wide variety of indications. Dosing is specific to the approved indication, and ranges from 100-750 mg orally every 12 hours for the tablet. For the IV formulation, the approved dose ranges from 200 to 400 mg every 8 to 12 hours.

The proposed dosing regimens for ciprofloxacin for inhalational anthrax (post-exposure) are given below:

Patient Population	Oral dose	Intravenous dose
Adult	500 mg Q12h x 60 days	400 mg (not to exceed 800 mg) Q12h
Pediatric*	10-15 mg/kg (not to exceed 500 mg per dose) Q12h x 60 days	10-15 mg/kg Q12h (not to exceed 800 mg per day)

* For children greater than 45 kg, the adult dosage should be used

Therapy should be initiated immediately after suspected or confirmed exposure and continue for 60 days.

III. CLINICAL PHARMACOLOGY SYNOPSIS

What pharmacokinetic data are available from monkeys infected with inhalational anthrax?

The study of ciprofloxacin to prevent inhalational anthrax was performed in a non-human primate (macaque) model and is supported by *in vitro* data assessing the activity of ciprofloxacin against *B. anthracis*. The authors also measured peak and trough serum concentrations of ciprofloxacin after administration of doses calculated by extrapolation from human doses.

Kelly, et al. Serum Concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. Journal Infect Dis 1992;166:1184-7.

Note: The raw ciprofloxacin data from this study can be found in Appendix 1.

Male and female adult monkeys were studied with a mean body weight of 7.7 kg (range 5.1 to 13.0 kg), and a mean body surface area of 0.46 m^2 [redacted] This represents a mean of 26% of the 1.73 m^2 body surface area of a 65-kg, 170-cm human. Ten animals were exposed to aerosolized anthrax spores and received a single ciprofloxacin 250 mg dose per nasogastric tube (pngt) 24 hours following exposure, followed twelve hours later by ciprofloxacin 125 mg pngt every 12 hours for 30 days. Blood samples for measurement of peak ciprofloxacin concentrations were collected on Days 5, 9, 20, and 30. Trough concentrations were collected on Days 3, 5, 9, and 20.

None of 10 monkeys treated with ciprofloxacin died from anthrax within the 30-day treatment period. One monkey died on Day 5 from accidental injection of drug into the lung.

Figures 1 and 2 below present individual (mean ± SD) peak and trough blood levels of ciprofloxacin, respectively, for during the 30-day period of drug administration. The MIC_{90} of ciprofloxacin for *B. anthracis* is also presented.

___1___ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

How does the exposure to ciprofloxacin in monkeys compare to humans?

Figures 3 and 4 (page 9) present individual (mean ± SD) serum or plasma concentrations of ciprofloxacin observed in the monkeys in the study performed by Kelly et al. compared with mean ± SD values obtained from the literature in a number of different human populations, including pediatrics. It should be noted that the pediatric data is derived from patients with cystic fibrosis (CF). It has been shown that the pharmacokinetics of ciprofloxacin in adult patients with CF are comparable to healthy adult subjects. Table 1 describes the populations and dosing regimens depicted in Figures 3 and 4.

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Table 5. Summary of Ciprofloxacin Pharmacokinetics from Various Literature Articles

Population	Dose/Regimen	Route	N	$C_{max,ss}$ (μg/mL) ± SD	$C_{min,ss}$ (μg/mL) ± SD	$AUC_{0-24,ss}$ (μg*h/mL) ± SD	Notes
Monkeys	250 mg x 1, then 125 mg po Q12h (*32 mg/kg x 1, then 16 mg/kg*)	PO	10	1.74 ± 1.41	0.17 ± 0.15	--	Loading dose of 2x used for 1st dose
Adults	500 mg Q12h (*7.1 mg/kg*)	PO	12	2.89 ± 0.54	0.28 ± 0.13	27.9 ± 5.72	At steady state
Adults	400 mg Q12h (*5.6 mg/kg*)	IV	--	4.56	0.2	25.4	At steady state
Human Males	400 mg x 1 (*5.6 mg/kg*)	IV	11	3.11 ± 0.61*	--	9.27 ± 1.51*	*Single dose, not at steady state
Obese Human Males	400 mg x 1 (*3.6 mg/kg*)	IV	17	2.66 ± 0.53*†	--	7.72 ± 1.49*	*Single dose, not at steady state
Peds, CF	10 mg/kg Q8h	IV	18	5.0 ± 1.5	0.39 ± 0.18	24.0 ± 6.4	Q8h dosing; different from proposed regimen
Peds, CF	20 mg/kg Q12h	PO	18	3.7 ± 1.4	0.42 ± 0.21	36.6 ± 12.0	Total dose 40 mg/kg; higher than proposed regimen
Peds, CF	10 mg/kg Q12h	IV	10	8.3	[redacted]	31.4	Similar to proposed regimen; levels obtained after 2nd IV dose (30 min infusion)
Peds, CF	15 mg/kg Q12h	PO	8	3.5	--	27.0	Similar to proposed regimen; levels obtained after 1st oral dose and preceded by two IV doses of 15 mg/kg over 30 min

CF- cystic fibrosis

†The C_{max} obtained after a single dose in obese human males is similar to that obtained after multiple dosing in adults of ideal body weight

Figure 3. Ciprofloxacin peak concentrations-animal and human studies

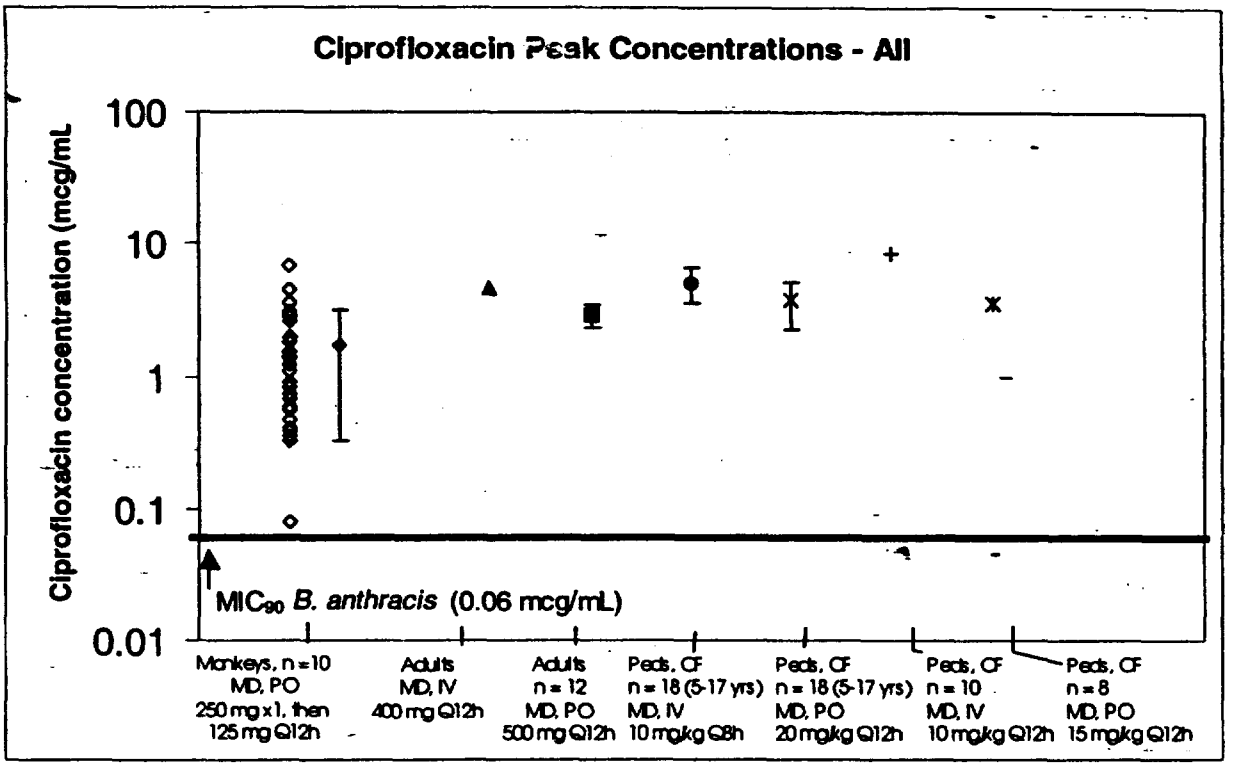
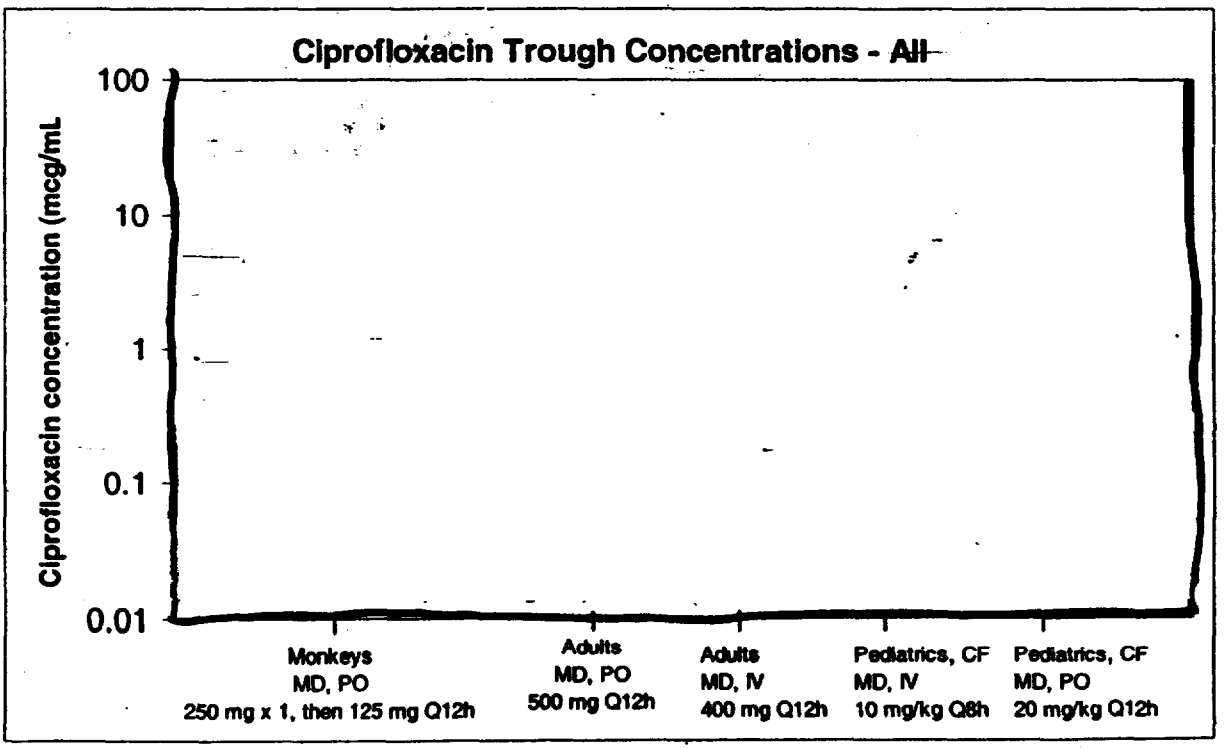


Figure 4. Ciprofloxacin trough concentrations-animal and human studies



Is there a pharmacokinetic/pharmacodynamic (PK/PD) relationship between ciprofloxacin exposure and efficacy in inhalational anthrax?

Fluoroquinolones, including ciprofloxacin, demonstrate concentration-dependent killing. The goal of a dosing regimen for these drugs is to maximize the serum concentrations. The peak concentration (C_{max})/MIC and/or AUC/MIC ratios are considered PK/PD parameters that best correlate with drug efficacy. Better correlation has been found with the AUC/MIC ratio than C_{max}/MIC, except possibly in infections where there is a significant risk of the emergence of resistant organisms. The relationship between these PK/PD parameters and drug efficacy has been demonstrated in animals models of infection as well as some clinical trials. Much of these data are derived from studies of infections with extracellular gram-negative organisms and in patients with nosocomial infections. Some recent data have demonstrated the usefulness of the AUC/MIC ratio for *Streptococcus pneumoniae.*

A comparison of pharmacokinetic with pharmacodynamic parameters in an animal model or human infection with inhalational anthrax cannot be made. *Bacillus anthracis* is gram-positive organism that exists intracellularly, so the optimal AUC/MIC or peak/MIC ratio is not known. In addition, there have been no prospective studies performed that link clinical outcome to drug exposure for this infection. However, in general when there is a demonstrated relationship between plasma concentrations of drug and response, pharmacokinetic data can be used as one way to characterize drug efficacy. Because of the unsuitability of performing a clinical trial in this particular infection, an alternative is to link the extent of ciprofloxacin systemic exposure in the animal model to what is seen in humans. As shown in Figures 3 and 4, the pharmacokinetics of ciprofloxacin in monkeys and humans are similar.

IV. GENERAL COMMENTS (NOT TO BE FORWARDED TO THE SPONSOR)

1. The sponsor has proposed a ciprofloxacin dose range of 10-15 mg/kg every 12 hours for pediatric patients treated with either IV or oral ciprofloxacin. In adults, a 500 mg oral dose given every 12 hours has been shown to produce an AUC equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 12 hours. In an ongoing study in pediatric patients with complicated urinary tract infections, ciprofloxacin is being initiated at a dose of 10 mg/kg IV every 12 hours, followed by 10-20 mg/kg orally every 12 hours.

   Therefore, the pediatric dosing recommendations for inhalational anthrax (post-exposure) will be modified, such that the IV dose will be 10 mg/kg infused over 60 minutes every 12 hours and the oral dose will be 15 mg/kg every 12 hours. Ciprofloxacin peak and trough concentrations obtained from pediatric patients administered this regimen, are consistent with what is seen in adults following 500 mg orally or 400 mg IV every 12 hours and are similar or in excess of the ciprofloxacin concentrations associated with survival in the monkey model.

V. LABELING RECOMMENDATIONS

1 page(s) of revised draft labeling has been redacted from this portion of the review.

VI. RECOMMENDATION

Based on what is known of the clinical pharmacology of ciprofloxacin, the clinical pharmacology/biopharmaceutics section of NDA 20-780/S-008 is acceptable and adequate to support approval.

/S/ 8/30/00

Joelle M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) /S/ 8/30/00

OCPB Briefing July 27, 2000 (attendees): Arzu Selen and Funmi Ajayi

cc: HFD-590: /NDA 20-780; SLR-008
/PM/JensenV
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HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ
HFD-205: FOI

APPENDIX 1: Ciprofloxacin Pharmacokinetic Monkey Data (Kelly et al 1992)

Cipro Trough - Monkeys

Monkey ID	Day 3	Day 5	Day 9	Day 20
82A35	0.1	0.07	0.08	0.08
358D	0.22	0.1	0.1	0.23
B7388	0.1	0.1	0.08	0.12
T292	0.42	0.43		
410D	0.08	0.07	0.05	0.04
A32	0.18	0.22	0.16	0.06
45Y	0.13	0.1	0.26	0.05
84456A	0.18	0.21	0.16	0.1
T308	0.45	0.31	0.27	0.83
40B	0.2	0.07	0.08	0.08
RANGE MIN				
MAX	0.45	0.43	0.27	0.83
GEOMEAN	0.18	0.14	0.12	0.11
MEAN	0.21	0.17	0.14	0.18
STDDEV	0.13	0.12	0.08	0.25

Cipro Peak - Monkeys

Monkey ID	Day 5	Day 9	Day 20	Day 30
82A35	0.91	0.56	0.39	0.39
358D	6.7	1.4	2.91	0.36
B7388	1.8	2.6	3.09	1.11
T292				
410D	0.08	2.6	3.57	1.8
A32	0.48	0.42	0.33	1.23
45Y	0.84	1.56	0.75	2.94
84456A	0.39	0.69	1.41	0.6
T308	1.98	2.91	4.47	1.56
40B	3.12	1.38	2.58	2.82
RANGE MIN				
MAX	6.7	2.91	4.47	2.94
GEOMEAN	0.98	1.29	1.55	1.12
MEAN	1.81	1.57	2.17	1.42
STDDEV	2.07	0.94	1.50	0.96

Reviewer's Comment: The mean ciprofloxacin concentrations achieved following dosing to steady state (expected C_{max} and trough) expressed in the label are based on a calculation of the geomentric mean as performed by the investigators (Kelly et al 1992). The numbers above were obtained from the raw data sheets and are slightly different due to difficulties in deciphering the numbers.

Steady State Parameters	*Geometric Mean Values (µg/mL)*	
	Kelly et al	*Reviewer's Analysis*
Expected C_{max}	*0.98 – 1.69*	*0.98 – 1.55*
Trough	*0.12 – 0.19*	*0.11 – 0.18*

APPENDIX 2: Literature Reference List

1. Gonzales MA, Uribe F, Moisen SD, et al. Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother 1984;26:741-4.

2. Peltola H, Ukkonen P, Saxen H, et al. Single-dose and steady-state pharmacokinetics of a new oral suspension of ciprofloxacin in children. Pediatrics 1998;101:658-62.

3. Rubio TT, Miles MV, Lettieri JT, et al. Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbation. Pediatr Infect Dise J 1997;16:112-7.

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6. Schaad UB, Salam MA, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. Pediatr Infect Dis J 1995;14:1-9.

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8. Neuman M. Clinical pharmacokinetics of the newer antibacterial 4-quinolones. Clin Pharmacokinet 1988;14:96-121.

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10. Reed MD, Stern RC, Myers CM, et al. Lack of unique ciprofloxacin pharmacokinetic characteristics in patients with cystic fibrosis. J Clin Pharmacol 1988;28:691-9.