FDA BRIEFING PACKAGE
ANTI-INFECTIVE DRUG PRODUCTS
ADVISORY COMMITTEE MEETING
JULY 28, 2000

Supplemental New Drug Applications 19-537, 19-847, 19-857, 19-858, 20-780
CIPRO (ciprofloxacin), Bayer Corporation Pharmaceutical Division, for post-exposure prophylaxis of clinical disease from inhaled *B. anthracis*

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INTRODUCTION

Background

Anthrax is a zoonotic infection that has been recognized as a human disease since antiquity. Cutaneous, gastrointestinal, and inhalational forms of infection with *B. 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 of post-exposure prophylaxis of disease caused by inhaled *B. anthracis* 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 scientific data supporting that application are the subject of the July 28, 2000 Anti-Infective Drug Products Advisory Committee meeting.

In February 1999, the first National Symposium on Medical and Public Health Response to Bioterrorism was held in Arlington, Virginia. This meeting recognized the lead role of the US Department of Health and Human Services in responding to the needs of a US population exposed to a biological agent. Disease surveillance, medical preparedness, and availability of appropriate pharmaceuticals and vaccines were noted as important elements of the public health response. As a member agency of the US Public Health Service, the responsibilities of the Food and Drug Administration include facilitation of the development of products that can be used to prevent, treat, or diagnose conditions caused by the exposure to an intentionally deployed biological agent.

In June 1999, the Centers for Disease Control and Prevention convened a panel of experts to identify the biological agents considered to be of greatest potential concern. The result was three categories of agents. The organisms in Category A were thought to be of greatest concern, warranting increased surveillance and the availability of appropriate therapy or prophylaxis for diseases caused by them (see Table 1).

Table 1-Biological agents-category A (US CDC, June 1999)

Organism	Disease
Variola major	Smallpox
Bacillus anthracis	Anthrax
Yersinia pestis	Plague
Clostridium botulinum toxin	Botulism
Francisella tularensis	Tularemia
Filoviruses/Arenaviruses	Hemorrhagic fever

Anthrax

Anthrax has been regarded as a possible agent of biowarfare or bioterrorism for almost a century. The inhalational form of the disease is considered the most likely clinical entity resulting from the intentional use of an aerosolized preparation of the spores of *B. anthracis.* Historically, penicillin has been the drug of choice to treat inhalational anthrax, but survival is poor once clinical manifestations are present. Mortality in inhalational anthrax is 80-100% in patients infected with penicillin-susceptible *B. anthracis* who receive appropriate treatment. The possibility of the use of a penicillin-resistant strain in an intentional attack has been raised. *For a discussion of epidemiology, microbiology, pathogenesis, clinical manifestations, prevention, and treatment of this infection, the reader is referred to the attached reprint of Pile et al, Anthrax as a potential biological warfare agent, Arch Intern Med 158: 429-34; Mar 9, 98.*

Among the Category A biological agents, inhalational anthrax is somewhat unique in that there was an outbreak of this infection in 1979 among the human population of Sverdlovsk, former USSR. This outbreak, considered the result of an accident at a military microbiology facility, is one of the few opportunities for systematic study of human disease resulting from any category A agent. *The reader is referred to the attached reprints Abramova et al, Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979, Proc Natl Acad Sci USA 90: 2291-94 March 1991 and Meselson et al, The Sverdlovsk anthrax outbreak of 1979, Science 266: 1202-08; Nov 18, 94.*

Regulatory status of drugs for anthrax

US government agencies seeking to make policy regarding appropriate drugs for treatment or prevention of disease in civilian or military populations must consider the regulatory status of those products. Government agencies either must use agents for which there is FDA-approved labeling for the clinical indication of interest, or are obliged to make an Investigational New Drug (IND) application to use an agent for an unapproved indication. If there are sufficient data to support approval of an indication, the preferred approach for drugs for which there is substantial clinical experience and a well-characterized safety profile is to approve labeling for the indication. Consideration of the data to support such an indication warrants careful weighing of risks and benefits.

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 for post-exposure prophylaxis for disease caused by inhaled *B. anthracis.*

Cipro for anthrax

The data under review for this Cipro application include cumulative human experience with ciprofloxacin. This drug was originally approved by FDA in 1987, and is currently approved for a wide variety of infections. The proposed regimen for oral ciprofloxacin for postexposure prophylaxis for inhalational anthrax is given below:

Patient population	Oral dose	Intravenous dose
Adult	500 mg q 12 h x 60 days	400 mg q 12 h
Pediatric	10-15 mg/kg q 12 h x 60 days	10-15 mg/kg q 12 h

Cipro in tablet form was approved for human use in the US in 1987; the intravenous solutions were approved in 1990. Dosing is specific to the approved indication, and ranges from 100-750 mg po q 12 hours for the tablet. For the intravenous formulation, the approved doses range from 200-400 mg iv q 12 hours. Cipro has been used by over 100 million patients. *The reader is referred to the attached package insert for Cipro, which lists the clinical indications and dosing regimens for which it has been approved.*

The study of ciprofloxacin to prevent inhalational anthrax was performed in a non-human primate (macaque) model; this is supported by *in vitro* data assessing the activity of ciprofloxacin against *B. anthracis. The reader is referred to the attached reprint of Friedlander et al, Postexposure prophylaxis against experimental inhalational anthrax, J Infect Dis 167: 1239-42, 1993.*

The discussion below begins with the microbiology of *B. anthracis*. It is followed by a review of the pharmacology of ciprofloxacin in the macaque with focus on differential tissue distribution. Macaque pharmacology is then compared with that of various human populations. The study under review (Friedlander et al, 1993) is discussed in the context of previous animal models of inhalational anthrax and epidemiologic studies of human experience. The discussion concludes with a review of pertinent aspects of the Cipro safety profile and efficacy in selected human infections.

MICROBIOLOGY - *B. anthracis*

Life cycle

Bacillus anthracis is a large gram-positive spore-forming rod. In clinical specimens, the organism appears as an encapsulated rod. In culture, it grows in a filamentous, unencapsulated form. Under certain conditions, it undergoes spore formation which permits the organism to survive under extreme conditions in the environment. Endospores are resistant to toxic chemicals including antimicrobial agents because their outer layers are highly impermeable. They are also heat resistant, and can survive heat exposures sufficient to denature solutions of proteins and nucleic acids. The water content of spores is extremely low. In the dehydrated state, proteins and nucleic acids become far more resistant to thermal denaturation.

Under certain favorable conditions, such as heat activation or the presence of certain chemicals, spores will start to germinate. If the necessary nutrients for growth are present, germination is followed by the conversion of the spore cell into a vegetative cell. The vegetative state of *B. anthracis* possesses two virulence factors. The presence of a polypeptide capsule confers resistance to phagocytosis; it is associated with the presence of a plasmid, pXO_2. The other virulence factor is the production of toxin, composed of three proteins which combine in pairs to produce two different effects. Protective antigen (PA) is necessary in combination with edema factor (EF) or lethal factor (LF) for the two latter toxins to cause tissue pathology. None of these three proteins has toxic effects by itself. Genes for all three are encoded on a plasmid, pXO_1.

Current hypotheses regarding the pathophysiology of inhalational anthrax suggest that inhaled spores are deposited on the pulmonary alveolar epithelium where they are phagocytosed by pulmonary macrophages, transported to local lymph nodes, and converted to the vegetative state. The reader is referred to sections below for a more detailed discussion of pathophysiology.

B. anthracis - *in vitro* susceptibility data

Traditionally *B. anthracis* is susceptible to drugs of the penicillin and tetracycline classes. In one study [Doganay M, Aydin N. Antimicrobial susceptibility of *Bacillus anthracis*. Scand J Infect Dis, **23:**333=335, 1991], twenty-two strains of *Bacillus anthracis* were isolated from cutaneous anthrax lesions in Turkey between 1981 and 1988. Minimum inhibitory concentrations (MICs) were determined by agar dilution. Mueller-Hinton agar was used and the inoculum was between 3×10^4 and 5×10^5 cfu/mL. Incubation was overnight at 37°C. Beta-lactamase production was also determined for each isolate. The results are shown below.

Table 2. Antimicrobial Susceptibility of 22 strains of *Bacillus anthracis*

Drug	MIC Range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Benzylpenicillin	0.015-0.03	0.015	0.015
Ampicillin	0.0125-0.03	0.03	0.03
Ampicillin/sulbactam	0.015-0.03	0.015	0.015
Ofloxacin	0.03-0.06	0.06	0.06
Ciprofloxacin	**0.03-0.06**	**0.06**	**0.06**

In another study [Lightfoot NF, Scott RJD, Turnbull PCB. Antimicrobial susceptibility of *Bacillus anthracis*. Salisbury Med Bull 68, Suppl**:** 95-98, 1990], seventy strains were tested in the United Kingdom. These strains were isolated from diverse areas over a long period of time. Agar dilution susceptibility testing was performed. Mueller-Hinton agar was used, the inoculum was 4.2×10^4 cfu/mL and incubation was at 37°C. Two strains were resistant to penicillin and produced a beta-lactamase constituitively. Three other strains could be induced to produce beta-lactamase. The results of this study are shown below.

Table 3. Antimicrobial Susceptibility of 70 strains of *Bacillus anthracis* (2)

Drug	MIC Range (μg /mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Penicillin	0.015-64	0.06	0.125
Amoxicillin	0.03-64	0.06	0.125
Tetracycline	0.06-1.0	0.125	0.125
Ciprofloxacin	**0.03-0.06**	**0.06**	**0.06**

The MIC_{90} value in both studies was 0.06 μg/mL. All tested isolates had MICs of 0.06 μg/mL or less.

***B. anthracis* -penicillin resistance**

In the study performed by Doganay et al it appears that all 22 strains were susceptible to penicillin since all isolates had MICs $\leq$0.03 μg/mL.

In the study performed by Lightfoot et al, which tested 70 strains, two strains were resistant with MICs of >0.25 μg/mL (Strains No. 32 and No. 70). Three strains showed strong beta-lactamase activity. These were strains No. 32 and No. 70, the penicillin-resistant strains, and No. 67, which was susceptible to penicillin and amoxicillin with MICs of 0.03 μg/mL. This is a resistant rate of 2.85% (2/70).

An epidemiologic study [Patra G, Vaissaire J, Weber-Levy M, Le Doujet C, Mock M. Molecular characterization of *Bacillus* strains involved in outbreaks of anthrax in France in 1997] found one penicillin-resistant strain among 11 strains isolated during outbreaks of anthrax in two different regions of France in 1997. This is about a 1% resistance rate but only a small number of strains were tested. This reference states that about 3% of naturally occurring anthrax strains overall are penicillin-resistant.

The rate of penicillin-resistance observed in *in vitro* studies of *B. anthracis* is consistent with observations from the published literature that state that about 3% of naturally occurring anthrax strains are resistant to penicillin. It has been reported that *B. anthracis* strains resistant to penicillin and tetracycline have been engineered by scientists in other countries. The possibility of penicillin and/or tetracycline resistance should be considered in the management of the patient exposed to aerosolized spores of *B. anthracis.*

CIPRO- ANIMAL PHARMACOLOGY
The data presented below summarize monkey pharmacology studies performed during the development of these two formulations:

Oral dosing-tissue levels in monkeys
Cipro tissue levels following 13 weeks of 15 mg/kg oral dosing:

Liver	1.0 Φg/g
Lung	0.1 to 0.3 Φg/g
Lymph nodes	0.1 to 0.3 Φg/g

Cipro tissue levels following 13 weeks of 45 mg/kg oral dosing:

Liver	3.3 Φg/g
Lung	0.3 to 0.9 Φg/g
Lymph nodes	0.3 to 0.9 Φg/g

Animals were sacrificed 24 hours after terminal dose (Week 13); no plasma data were reported. Actual lung and lymph node values were not specified but fell within the listed ranges.

Intravenous dosing-tissue and blood levels in monkeys

Table 4. Tissue Ciprofloxacin Concentrations (24 Hours Post-Dosing at Week 26)

	Tissue Concentrations (Φg/g or Φg/ml)		
Tissues	5 mg/kg	10 mg/kg	20 mg/kg
Liver	0.11	0.34	1.0
Spleen	0.15	0.16	0.3
Lymph Nodes	0.13	0.42	1.1
Plasma*	-	-	0.1

* In separate segment of this study a 24-hour post-infusion plasma sample was analyzed following a 20 mg/kg dose; the ciprofloxacin concentration was approximately 0.1 Φg/ml.

Although the studies cited above vary in dosing regimens, sampling times, and tissues sampled and therefore cannot be compared directly, a few salient points can be noted. Following 13 weeks of oral dosing, animals that received ciprofloxacin 15 mg/kg were found to have drug levels in the liver that were approximately 3-10x that in the lung or lymph node. Tissue levels resulting from 3x this dose were 3x as high as those observed in the 15 mg/kg group, and the differential tissue distribution observed in the 45 mg/kg group were similar to those seen in the lower dose group.

Differential tissue distribution was seen in animals in the repeat dose intravenous study, but this was only observed in those animals that received 20 mg/kg. Interestingly, both liver and lymph nodes were found to have drug levels that were ~3x that seen in the spleen. The intravenous studies also provide a means to compare plasma levels with drug levels found in the various organs of the reticuloendothelial system, the site of much of the early pathology noted following infection with inhaled *B. anthracis*. Following a 20 mg/kg dose, lymph node and liver drug levels were found to be ~10x that of plasma; spleen drug levels were similar to that of plasma.

The animals studied in the experiment under review were macaques 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 (range 0.35 to 0.65 m^2). This represents a mean of 26% of the 1.73 m^2 body surface area of a 65-kg, 170-cm human. The animals exposed to aerosolized anthrax spores received a single ciprofloxacin 250 mg dose per nasogastric tube (pngt) 24 hours following exposure, followed twelve hours later by ciprofloxacin 125 mg pngt q 12 hours for 30 days. Figures 1 and 2 below present individual (mean ± SD) peak and trough blood levels of ciprofloxacin, respectively for these animals during the 30-day period of drug administration. The MIC_{90} of ciprofloxacin for *B. anthracis* is also presented.

Figure 1. Ciprofloxacin trough concentrations (Friedlander et al, 1993)

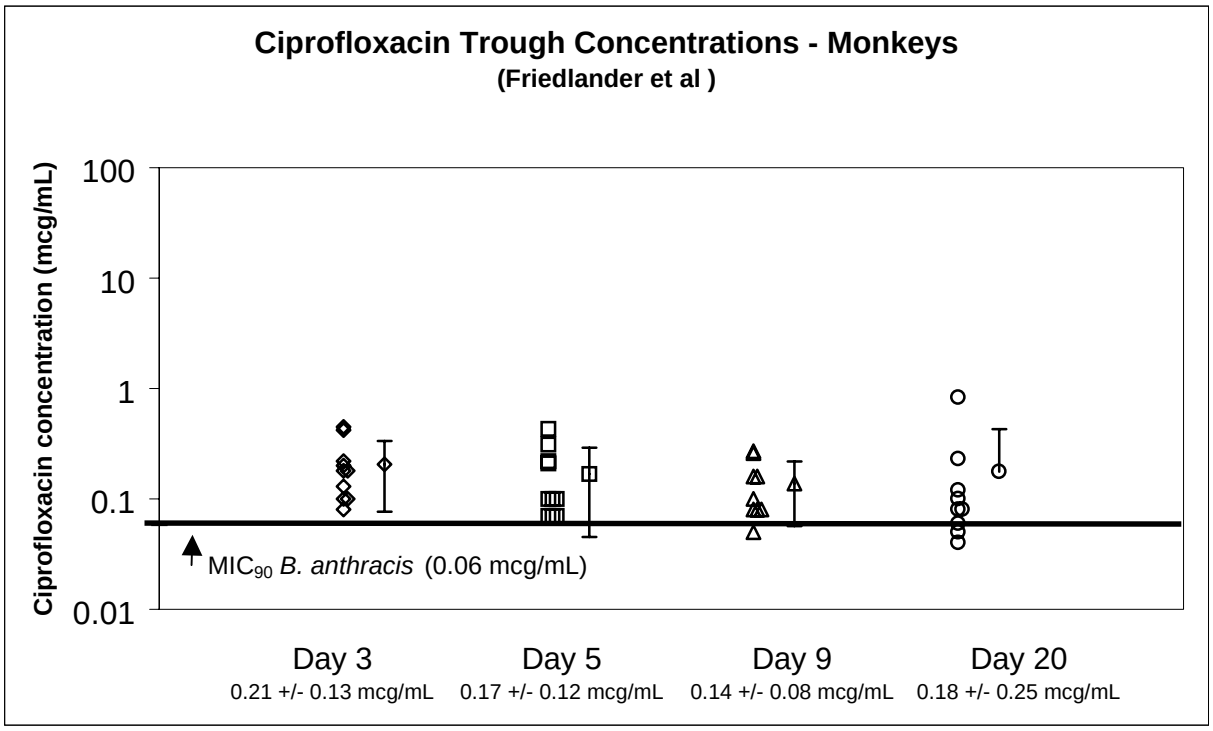
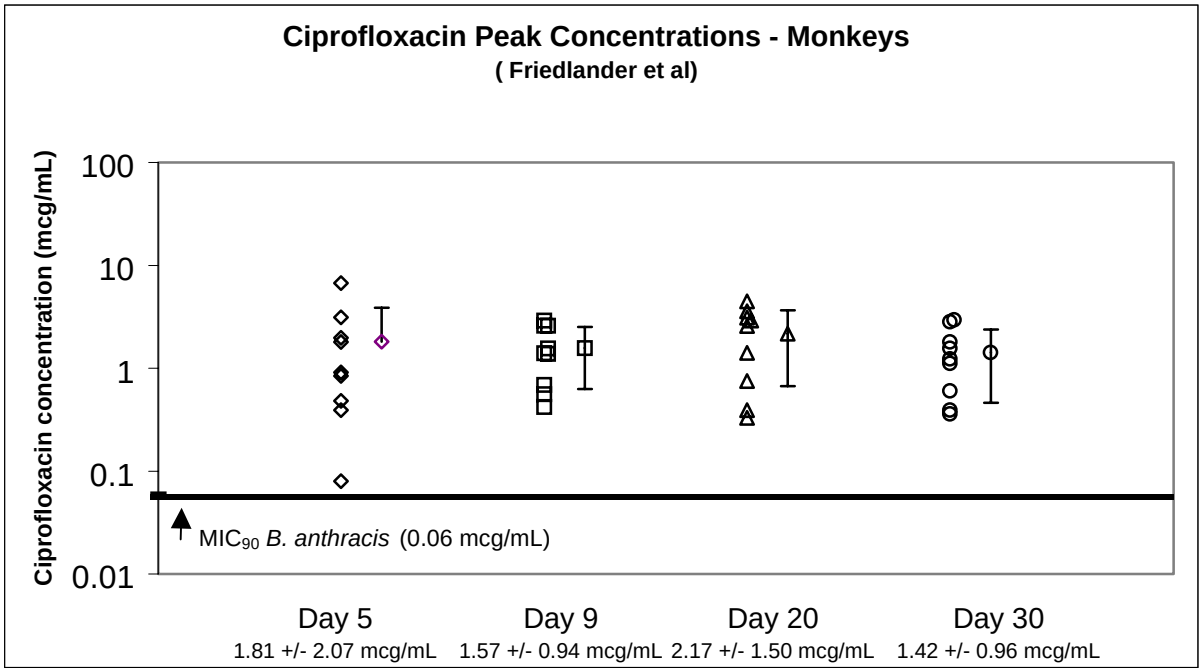


Figure 2. Ciprofloxacin peak concentrations (Friedlander et al, 1993)



CIPRO-COMPARISON OF ANIMAL AND HUMAN PHARMACOLOGY

The graphs below present individual (mean ± SD) blood levels of ciprofloxacin observed in the monkeys in the study performed by Friedlander 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). However, the pharmacokinetics of ciprofloxacin in this patient population is known to be comparable to healthy subjects. Table 5 describes the populations and dosing regimens depicted in Figures 3 and 4.

Table 5. Summary of Ciprofloxacin Pharmacokinetics

Population	Dose/Regimen	Route	N	$C_{max,ss}$ (μg/mL) ± SD	$C_{min,ss}$ (μg/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**	**--**	**2.97**	**0.2**	**At steady state**
Adults	400 mg Q12h (*5.6 mg/kg*)	IV	--	4.56	0.2	At steady state
Human Males	400 mg x 1 (*5.6 mg/kg*)	IV	11	3.11 ± 0.61*	--	*Single dose, not at steady state
Obese Human Males	400 mg x 1 (*3.6 mg/kg*)	IV	17	2.66 ± 0.53*[H]	--	*Single dose, not at steady state
Peds, CF	10 mg/kg Q8h	IV	18	5.0 ± 1.5	0.6 ± 0.58	Q8h dosing; different from proposed regimen
Peds, CF	20 mg/kg Q12h	PO	18	5.9 ± 3.7	0.42 ± 0.21	Total dose 40 mg/kg
Peds, CF	10 mg/kg Q12h	IV	10	8.3	--	Similar to proposed regimen
Peds, CF	15 mg/kg Q12h	PO	8	3.5	--	Similar to proposed regimen

CF- cystic fibrosis

[H]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. Cipro peak concentrations-animal and human studies

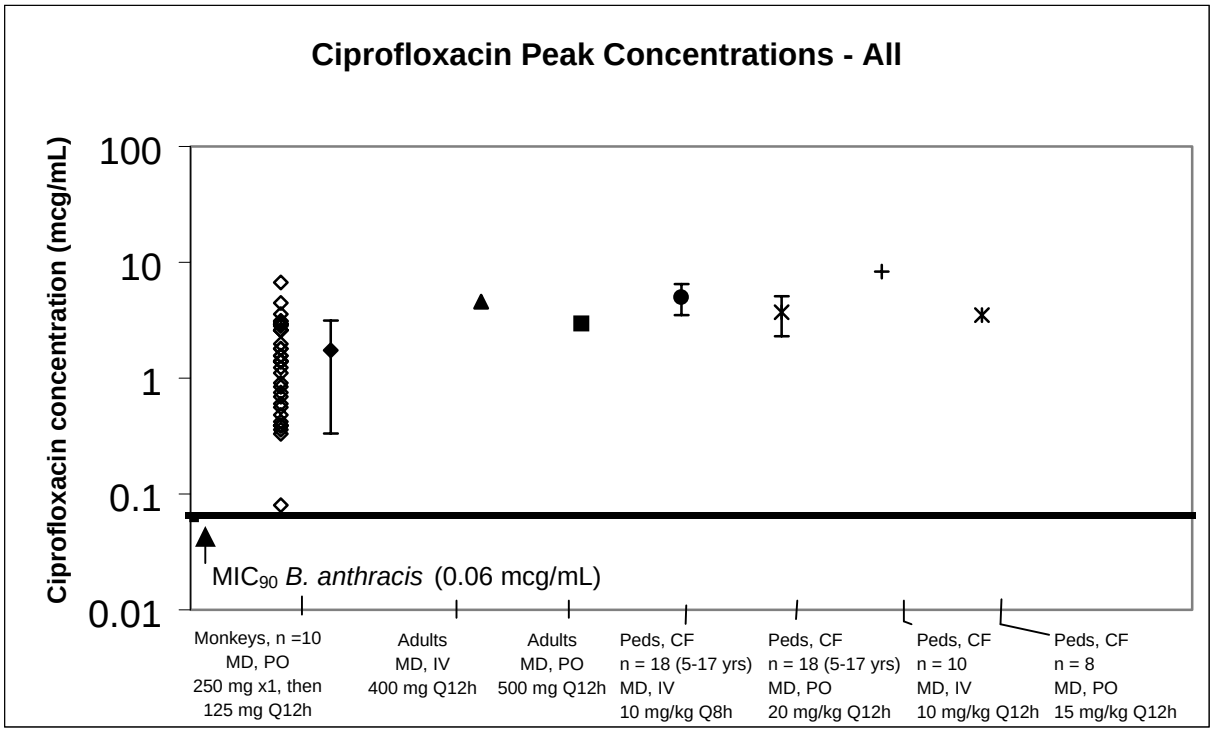
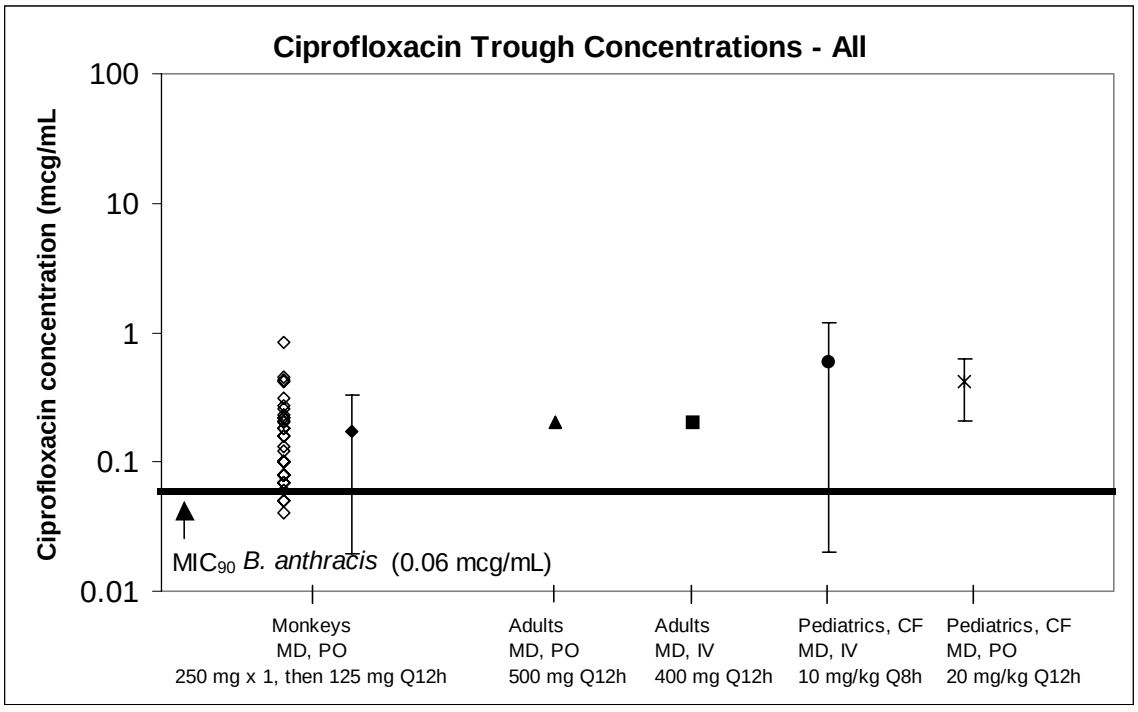


Figure 4. Cipro trough concentrations-animal and human studies



Pharmacokinetics/Pharmacodynamics (PK/PD)

Fluoroquinolones demonstrate concentration-dependent killing. The goal of a dosing regimen for these drugs is to maximize the plasma concentrations. The peak concentration (Cmax)/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 Cmax/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 and Cmax/MIC ratio for *Streptococcus pneumoniae*. Studies of PK/PD parameters for this gram-positive organism suggest that Cmax/MIC values $\geq$8-12 correlate with clinical efficacy.

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 may be used as one way to relate dose and possible outcome. A direct comparison of pharmacokinetic and pharmacodynamic parameters in an animal model of inhalational anthrax cannot be made. The optimal AUC/MIC or peak/MIC ratios for the treatment of infection due to *B. anthracis* not known. However, it is useful to compare the achievable blood levels in humans with the proposed dosing regimen and the blood levels in the macaque model. As shown in Figures 3 and 4, the pharmacokinetics of ciprofloxacin in monkeys and humans are similar. Ciprofloxacin peak concentrations achieved with repeat dosing regimens studied in macaques are ~33x MIC_{90} for *B. anthracis*. In humans, peak concentrations are ~50x MIC_{90} for *B. anthracis.*

INHALATIONAL ANTHRAX-
ANIMAL MODELS AND HUMAN EPIDEMIOLOGY

Since the 1940s, study of the interactions between host and pathogen in inhalational anthrax has been undertaken in a number of animal models. Epidemiologic studies have provided insight into the development of industrial disease in humans. The following discussion presents the findings of some of this earlier work in the context of the current application. This discussion will focus on those results from previous animal experiments that address questions that arise when considering the post-exposure administration of an antimicrobial to the human host exposed to aerosolized *B. anthracis.*

Inhalational anthrax was only described as a clinical entity in the mid-nineteenth century, when it was noted to be a serious public health problem among workers in the British textile industry. There were initially two theories on the pathogenesis of this infection. One was that the inhaled spores were phagocytosed by pulmonary macrophages and transported to the mediastinum where they germinated and produced toxin. The other theory was that the portal of entry was an erosion of the bronchial mucosa which then permitted the development of pneumonia by the vegetative stage of the organism. Henderson, Peacock, and Belton attempted to address this question in a study of penicillin prophylaxis in a macaque model of pulmonary anthrax. They hypothesized that if the first model of pathogenesis were correct, then penicillin might only be effective for as long as it was being administered and until the spores were completely removed from the lung. If the second were operative, then administration of an antimicrobial might effectively eradicate the organism and prevent disease entirely. *The reader is referred to the attached reprint, Henderson et al, Observations on the prophylaxis of experimental pulmonary anthrax in the monkey, J Hyg 54: 28-36, 1956 for a full description of this study.*

Penicillin administration that began 24 hours after exposure to aerosolized spores of *B. anthracis* and continued for five days was shown to only delay death in the animals exposed [Henderson et al, Fig 1]. When the duration of penicillin was extended to 10 or 20 days, a similar delay of death was observed, and the length of time by which death was delayed was generally proportional to the duration of antimicrobial administration [Henderson et al, Fig 2]. Passive immunization with hyperimmune horse serum after exposure to aerosolized spores again resulted in a similar delay of death and, like the penicillin groups, in survival curves that were largely parallel to those of the control (untreated) animals [Henderson et al, Fig 3]. The authors then investigated the efficacy of the combination of active immunization with soluble protective antigen and penicillin, both given 24 hours after exposure. Penicillin was administered for five days. Survival curves for this experiment [Henderson et al, Fig 4] showed that protection was conferred equally well by active immunization prior to exposure or by penicillin and active immunization after exposure. Animals who received a 5-day course of penicillin only demonstrated the same rapid drop in survival as was demonstrated in the earlier short-course penicillin experiments. The authors then introduced the question of spore retention when they questioned whether transitory modes of prophylaxis would be effective in the prevention of inhalational anthrax if spores could survive for such long periods. They

noted that only a small proportion of spores was ultimately deposited in local lymph nodes; others were detected in the lung parenchyma 100 days after exposure. They also quantified the proportion of spores that were found in the lungs following exposure, and produced the following table:

Table 6. Retention of *B. anthracis* spores in the lung following aerosol challenge (2-8 x 10^5 spores/L) [Henderson et al 1956]

Time after exposure (days)	Estimated % of original retention
42	15-20
50	2
75	0.5-1
100	traces

Thus the idea of spore attrition was introduced. Small numbers of spores could be found as long as 100 days after exposure. The work of Henderson's group supported the idea of 'dormant infection,' and demonstrated a number of antimicrobial regimens that were too short to successfully protect the exposed macaque from inhalational anthrax. These experiments also invoked the concept of 'spore clearance,' suggesting that there existed a mode of exit from the lung for *B. anthracis* spores other than phagocytosis and subsequent development into the pathogenic vegetative state.

Other early studies of inhalational anthrax in the guinea pig by Ross permitted direct observation of spores deposited on pulmonary alveolar epithelium, and provided insight into possible mechanisms of 'spore attrition.' Ross noted that the number of spores that reached regional lymph nodes was substantially less than the number deposited on the alveolar epithelium. Using staining techniques that differentiated heat-stable and heat-labile spores, maturing spores, and bacilli, she demonstrated that some inhaled spores that were deposited on the alveolar epithelium were picked up by pulmonary macrophages, transported to regional lymph nodes, developed into vegetative organisms in the reticuloendothelial system (RES) and thus produced toxin and systemic disease. Other phagocytosed spores were shown to pass into the bronchioles and presumably leave the lung by the airways, and still others may have reached a stage of maturation in the macrophage that permitted spore lysis and destruction within the phagocytic cell. While only a rough quantification of inhaled spores was possible with Ross' experiments, she provided histologic evidence that not all inhaled spores develop into vegetative organisms that produce systemic disease. *The reader is referred to the attached reprint, Ross, The pathogenesis of anthrax following the administration of spores by the respiratory route, J Path Bact 73: 495-494, 1957.*

The experimental data submitted in the regulatory application under discussion are summarized in the attached reprints, Friedlander et al, Postexposure prophylaxis against experimental inhalational anthrax, J Infect Dis 167: 1239-42, 1993 and Kelly et al, Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. Inspection of the survival curves [Friedlander et al, Fig 1] suggests that a number of different regimens studied in this series of experiments afford comparable protection following the first challenge. Tables 7 and 8 below present

statistical analyses of mortality rates in animals receiving Cipro compared to animals in each of the other treatment groups. While the small sample sizes result in wide confidence intervals, mortality rates for the Cipro cohort are similar to mortality rates for penicillin, doxycycline, and doxycycline plus vaccine cohorts for both the intent to treat (ITT) and evaluable study populations.

Table 7. Evaluable Population Analysis: cause of death proven to be due to anthrax

Treatment	Anthrax deaths	P vs. control[I]	95%o CI of treatment - control	95%o CI of ciprofloxacin–comparator
Control untreated	9/10			
Vaccine alone	8/10	> 0.1	(-54.1%, 37.2%)	(-96.8%, -23.9%)
Penicillin	3/10	0.0198	(-88.7%, -12.3%)	(-67.5%, 24.0%)
Ciprofloxacin	1/9*	0.0011	(-97.5%, -35.0%)	
Doxycycline	1/10	0.0011	(-97.6%, -36.2%)	(-42.9%, 50.5%)
Doxycycline + vaccine	0/9[H]	0.0001	(-99.8%, -51.6%)	(-37.4%, 56.3%)

*One animal died 5 days after exposure from aspiration pneumonia, had no evidence of anthrax at autopsy, and was excluded from the evaluable population for this analysis. Another animal died 73 days after antibiotic treatment. Therefore, though this animal was evaluable, this death was not thought to be anthrax related and was not included in this analysis.

[H]One animal died 6 days after discontinuing doxycycline with no evidence of anthrax on autopsy. Cause of death remains unknown: the animal was excluded from this statistical analysis.

[I] P-value was calculated using a two-tailed Fisher's exact test.

o 95% confidence interval was calculated using an exact method.

Table 8. ITT Analysis: including all cause of death as failure

Treatment	All deaths	P vs. control[I]	95%o CI of treatment - control	95%o CI of ciprofloxacin – comparator
Control untreated	9/10			
Vaccine alone	8/10	> 0.1	(-54.1%, 37.2%)	(-82.9%, -1.4%)
Penicillin	3/10	0.0198	(-88.7%, -12.3%)	(-45.9%, 45.9%)
Ciprofloxacin	3/10	0.0198	(-88.7%, -12.3%)	
Doxycycline	1/10	0.0011	(-97.6%, -36.2%)	(-28.3%, 62.0%)
Doxycycline + vaccine	1/10	0.0011	(-97.6%, -36.2%)	(-28.3%, 62.0%)

[I] P-value was calculated using a two-tailed Fisher's exact test.

o 95% confidence interval was calculated using an exact method.

Underlying the consideration of a post-exposure prophylaxis regimen of ciprofloxacin is the question of the duration of drug administration. The early studies by Henderson and others demonstrated that regimens of 5, 10, and 20 days were too short; high mortality was only delayed. Review of the Friedlander data from the initial challenge phase of the survival curves suggests that a regimen of 30 days results in survival rates that begin to approximate the 'best case' results. However, among the animals that received

ciprofloxacin was one that died of anthrax six days after the completion of drug administration. One of ten animals in this cohort was not sufficiently protected from inhalational anthrax following 30 days of ciprofloxacin alone. This suggests there were an adequate number of inhaled spores remaining to result in some proportion progressing to the vegetative phase, producing toxin, and causing disease after 30 days of antimicrobial alone. Data from the largest human outbreak in Sverdlovsk, 1979 show that one patient developed disease 43 days after the presumed exposure. Given the possibility that there exist (s) some mechanism (s) of spore attrition over time, might there be a 'floor' to the spore load in the lung below which inhalational anthrax is unlikely to occur? If such a floor exists, is there a period of antimicrobial administration that will eradicate enough of the developing vegetative organisms such that the risk of disease is minimized?

Table 6 gave a rough approximation of spore load with the passage of time following exposure to aerosolized *B. anthracis* spores. It suggests that after 50 days post-exposure there are far fewer spores in the lungs than the original inhaled load. However it does not quantify the spore load, nor does it speculate about the number of spores that are sufficient for the development of clinical disease. Epidemiologic studies of mill workers with industrial exposure to anthrax spores provide some insight into this question. The aerosol infective dose for man is thought to be relatively high. Air sampling in animal-hair mills demonstrated that nonimmunized workers inhaled between 150-700 anthrax-contaminated particles with a diameter of 5 μ or less during a single eight hour shift, but clinical anthrax was rare in those mills. Other investigators recovered *B. anthracis* from the nose and pharynx of 14 of 101 healthy workers in two goat hair mills. Thus the possibility exists that there is a low organism load that is not associated with clinical disease [Knudson, Treatment of anthrax in man: history and current concepts, Military Med 151: 71-77, Feb 1986].

One might consider repeated low-level exposures in the workplace a different immunologic challenge than the exposure resulting from an intentional exposure to aerosolized anthrax spores. Perhaps the occupational exposures present enough antigen to elicit a protective immune response over time. Epidemiologic studies suggest that this is not the case. Brachman and Fekety compared the length of employment in goat-hair processing mills of a group of employees without a history of anthrax with the length of employment of those who did. They found that the likelihood of the development of anthrax was independent of the length of time of employment in the mill. This suggested that repeated low-level occupational exposures to anthrax spores do not confer protection against disease [Brachman and Fekety, Industrial anthrax, Annals NY Acad of Sci, 70:574-84, 1958].

The possibility exists that a relatively small load of inhaled anthrax spores can be carried asymptomatically by the unimmunized human host. The eradication of vegetative organisms that results from the administration of ciprofloxacin plus clearance route (s) for inhaled spores that do not result in toxin elaboration and disease raise the question of the appropriate duration of drug administration following exposure to aerosolized spores of *B. anthracis*.

The prophylactic administration of an antimicrobial following exposure to an aerosol challenge is an effort to reduce risk of the development of clinical disease. Experimental and epidemiologic data cited above suggest that a prophylactic regimen following exposure to aerosolized *B. anthracis* should be dosed for at least 45 days. At some period following that point, organism load in the lung passes a threshold below which disease is unlikely. The duration proposed for the administration of ciprofloxacin following exposure to aerosolized anthrax spores is 60 days.

CIPROFLOXACIN-SAFETY PROFILE

Cipro has been marketed in the US since 1987. Estimates of use in the US exceed 100 million prescriptions. Consideration of a post-exposure prophylaxis regimen for the inhalational anthrax warrants attention to certain aspects of the safety database, prolonged use regimens (≥ 30 days) and pediatric use. *The reader is referred to the attached reprints, Segev et al, Safety of long term therapy with ciprofloxacin, Clin Infect Dis 28: 299-308, 1999 and Hampel et al, Ciprofloxacin in pediatrics, Pediatr Infect Dis J, 16: 127-9, 1997 for a discussion of these data*.

The development of fluoroquinolones for pediatric use has been an issue of discussion since 1989. Most recently, the issue was presented before this advisory committee in November 1997, when the consensus was that pediatric development of fluoroquinolones was warranted for serious and life threatening infections. These included indications such as meningitis, fever and neutropenia, and complicated urinary tract infection [Anti-Infectives Advisory Committee minutes, 62nd meeting Nov 19, 1997].

CIPROFLOXACIN-EXPERIENCE IN SELECTED HUMAN INFECTIONS

The efficacy profile of ciprofloxacin for the indication under discussion might be further characterized by information regarding ciprofloxacin treatment of human cases of anthrax as well as ciprofloxacin treatment of related infections. Data on ciprofloxacin treatment of human infections with *B. anthracis* and of mediastinitis due to a ciprofloxacin-susceptible organism are limited to case reports. A search of the medical literature provided one report of the successful treatment of a patient with *B. anthracis* sepsis following an extensive cutaneous infection. This patient received intravenous penicillin and ciprofloxacin as well as steroids for two weeks, then completed therapy with oral ciprofloxacin for an additional two weeks [Felek et al, A case of anthrax sepsis: non-fatal course, J Infect 38:201-2 May 1999]. Another report documents the successful use of imipenem, ciprofloxacin, and surgical debridement in a patient with postoperative *Nocardia mediastinitis* [Thaler et al, Mediastinitis due to *Nocardia asteroides* after cardiac transplantation, Intensive Care Med 18: 127-8, 1992].

Cipro has an approved indication for the treatment of lower respiratory tract infection due to *E. coli, K. pneumoniae, E. cloacae, P. mirabilis, P. aeruginosa, H. influenzae, H. parainfluenzae*, and (not a drug of first choice) *S. pneumoniae.* Cipro also has an indication for the treatment of an infection of the reticuloendothelial system, typhoid fever due to susceptible strains of *S. typhi* and *S.paratyphi*.