CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S038

19-847/S024

19-857/S027

19-858/S021

20-780/S008

ADMINISTRATIVE DOCUMENTS

Exclusivity Checklist

NDA: 19-537/S-038, 19-847/S-024, 19-857/S-027, 19-858/S-021, 20-780/S-008				
Trade Name: Cipro®				
Generic Name: Ciprofloxacin hydrochloride tablets, IV solution, IV in 5% Dextrose, IV in 0.9% NS, and oral suspension				
Applicant Name: Bayer Corp., Pharmaceutical Division				
Division: HFD-590 Div. of Special Pathogen and Immun. Drug Products				
Project Manager: Valerie Jensen				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	SE1			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes		No	X
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation: This indication is based on the use of a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans. It is approved under accelerated approval regulations 21CFR 314.510				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	X
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES N/A				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				

NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	X

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:				
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):	
Investigation #1	
Investigation #2	
Investigation #3	

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	

IND#:				
Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

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Signature of PM/CSO
Date: 8/16/00 /S/

Signature of Division Director
Date: 8/28/00 /S/

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

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Debarment Certification Not Applicable

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	019537	**Trade Name:**	CIPRO (CIPROFLOXACIN HCL) TABLETS
Supplement Number:	038	**Generic Name:**	CIPROFLOXACIN HYDROCHLORIDE
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	ANTIBACTERIAL, QUINOLINE
Action Date:	3/1/00		

Indication # 1 Inhalational anthrax (post exposure)
Label Adequacy: Adequate for ALL pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any):

Lower Range	Upper Range	Status	Date
0 years	16 years	Deferred	1/1/04

Comments: Deferring submission of the final study report for long term observational study currently underway (8/25/00). Pediatric labeling granted for 0-16yr at time of this approval.

This page was last edited on 8/25/00

/S/ 8/25/00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	019847	**Trade Name:**	CIPRO (CIPROFLOXACIN) IV 1% VIALS & AMPS
Supplement Number:	024	**Generic Name:**	CIPROFLOXACIN
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	ANTIBACTERIAL AGENT FOR LOWER RESPIRATORY INFECTIONS.
Action Date:	3/2/00		

Indication # 1 Inhalational anthrax (post exposure)
Label Adequacy: Adequate for ALL pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any):

Lower Range	Upper Range	Status	Date
0 years	16 years	Deferred	1/1/04

Comments: Deferring submission of the final study report for long term observational study currently underway (8/25/00). Pediatric labeling granted for 0-16yr at time of this approval.

This page was last edited on 8/25/00

Signature - /S/ _____ 8/25/00 Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	019858	**Trade Name:**	CIPRO (CIPROFLOXACIN) IN SODIUM CHLORIDE
Supplement Number:	021	**Generic Name:**	CIPROFLOXACIN
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	ANTIBACTERIAL AGENT FOR LOWER RESPIRATORY INFECTIONS.
Action Date:	3/2/00		

Indication # 1 Inhalational anthrax (post exposure)
Label Adequacy: Adequate for ALL pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any):

Lower Range	Upper Range	Status	Date
0 years	16 years	Deferred	1/1/04

Comments: Deferring submission of the final study report for long term observational study currently underway (8/25/00). Pediatric labeling granted for 0-16yr at time of this approval.

This page was last edited on 8/25/00

/S/ 8/25/00

Signature - Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020780	**Trade Name:**	CIPRO (CIPROFLOXACIN) ORAL SUSPENSION
Supplement Number:	008	**Generic Name:**	CIPROFLOXACIN
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	ALL CIPRO TABLET INDICATIONS
Action Date:	3/2/00		

Indication # 1 Inhalational anthrax (post exposure)
Label Adequacy: Adequate for ALL pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any):

Lower Range	Upper Range	Status	Date
0 years	16 years	Deferred	1/1/04

Comments: Deferring submission of the final study report for long term observational study currently underway (8/25/00). Pediatric labeling granted for 0-16yr at time of this approval.

This page was last edited on 8/25/00

Signature - V. /S/ — Date 8/25/00

DIVISION DIRECTORS' MEMORANDUM

NDAs:	19-537/S-038 (ciprofloxacin tablets) 20-780/S-008 (ciprofloxacin oral suspension) 19-858/S-021 (ciprofloxacin IV solution) 19-847/S-024 (ciprofloxacin IV in 5% dextrose) 19-857/S-027 (ciprofloxacin IV in 0.9% saline)
Indication:	Inhalational anthrax (post-exposure)
Trade Name:	Cipro®
Applicant:	Bayer Corporation Pharmaceutical Division
Submission Dated:	February 29, 2000
Date of Memorandum:	August 29, 2000

SUPPLEMENTAL APPLICATIONS FOR INHALATIONAL ANTHRAX (POST-EXPOSURE):

This memo summarizes key information on

A) Ciprofloxacin
B) Anthrax
C) The monkey model of inhalational anthrax (post-exposure)
D) July 28, 2000 Advisory Committee recommendations
E) Scientific and Regulatory basis for the approval of ciprofloxacin for inhalational anthrax (post-exposure).

The information has been extracted from the FDA approval package for these applications, the background material provided to the Advisory Committee and the July 28, 2000, advisory committee meeting/transcript. Also referred to within this memo are sections of the CFR, Federal Register, and previous public advisory committee meetings.

INTRODUCTION:

At the express request of the Food and Drug Administration (FDA), Bayer Corporation Pharmaceutical Division (Bayer) submitted efficacy supplements to their NDAs for the use of ciprofloxacin in inhalational anthrax (post-exposure). FDA requested these supplements because *Bacillus anthracis*, the bacterium that causes post-exposure inhalational anthrax, is considered to be one of the most likely biological weapons that could be used intentionally in a wartime or other conflict situation. At present, there are no drugs approved specifically for inhalational anthrax (post-exposure). Of note, penicillin and doxycycline currently list *B. anthracis* in their labeling. This means that

although not approved specifically for inhalational anthrax, these drugs may be used in post-exposure inhalational anthrax and such use would be considered within the scope of the labeled *B. anthracis* indication. However, if penicillin-resistant and doxycycline-resistant strains of *B. anthracis* were to be engineered, alternative agents would need to be available.

CIPROFLOXACIN :

General Information:

Ciprofloxacin is a fluoroquinolone antimicrobial, available in five formulations. Cipro® Tablets were approved in 1987, Cipro® IV formulations were approved in 1990 and Cipro® Oral Suspension was approved in 1997.

Efficacy:

Ciprofloxacin is approved for a broad range of indications caused by designated susceptible gram-positive and gram-negative bacteria, including acute self-limited infections and more serious, life-threatening infections. Some of these include respiratory tract infections, nosocomial pneumonia, urinary tract infections, skin and skin structure infections, infectious diarrhea, gonorrhea, chronic bacterial prostatitis and empiric treatment of patients with fever and neutropenia.

Dosing:

Approved doses range from 100 – 750 mg/day orally; usual doses are 500 mg q12 hours. The oral formulation is approximately 80% bioavailable relative to the IV formulations. The IV regimens approved are 200 or 400 mg q12h (or q8h for more serious infections). Although to date the drug has not been approved for use in pediatric patients, information on the pharmacokinetics of ciprofloxacin in pediatric patients with cystic fibrosis is available for 10 and 15 mg/kg doses. Ciprofloxacin dosing is approved for use up to durations of 28 days (prostatitis) and 6 weeks (bone and joint infections).

Pharmacokinetics:

Following oral ciprofloxacin doses of 500 mg q12h PO, Cmax = 2.89 mcg/mL, Cmin = 0.28 mcg/mL and AUC = 27.9 mcg*hr/mL. After IV dosing, peaks are higher while troughs and AUC are comparable. Pediatric patients given 15 mg/kg q12h PO reach Cmax= 3.5 mcg/mL and AUC = 27 mcg*hr/mL. These levels are relevant when compared to the ciprofloxacin serum levels measured in the nine monkeys in the animal efficacy study (see below).

Safety:

Since its introduction in 1987, ciprofloxacin has been given to 250 million people in the world, including 100 million in the US. The approved courses of therapy range from

single doses in gonorrhea, three-day treatment of cystitis, 7-14 day treatment of respiratory and skin infections, 28 days for prostatitis and 6 weeks for bone and joint infection. Based on the extensive use and review of information, it may be concluded that the Cipro® safety profile has been well characterized. The most common adverse events are nausea, diarrhea, vomiting, abdominal pain, restlessness, CNS disturbances, rash, headache, hepatic enzyme abnormalities. The most frequent post-marketing adverse events were: rash, tendon disorder, arthralgia, pruritus, urticaria, nausea, diarrhea, convulsion, liver function test abnormality, dizziness, photosensitivity reaction.

Rationale for developing ciprofloxacin for this indication – COMMENTS:

Ciprofloxacin has been available and used for over 13 years in treating a wide range of infections. Its demonstrated safety and efficacy profile made it a rational choice for evaluation in post-exposure inhalational anthrax, an indication where it is clear that adequate and well-controlled clinical trials in the specific indication could not be conducted.

Long-term use: Additional information, including information presented by Bayer at the July 28, 2000, AntiInfective Advisory Committee meeting (see below) indicates that at least one thousand patients have received treatment of 60 days or longer in Bayer trials. Analysis of these data indicates that no unexpected or more serious adverse events were identified.

Pediatric Use: Fluoroquinolones, including ciprofloxacin, are currently not indicated for the treatment of any pediatric infections because these agents, as a class, have been shown to cause arthropathy in weight-bearing joints of juvenile animals, particularly dogs. However, it is recognized that off-label use of fluoroquinolones in pediatrics has occurred. In fact, the evaluation of fluoroquinolones in pediatrics was the subject of Anti Infective Advisory Committee meetings in 1993 and 1997. During the 1993 meeting, the Agency was advised that pediatric studies of fluoroquinolones were warranted in children with cystic fibrosis and malignancies; during the 1997 meeting, the Agency was advised that pediatric studies of fluoroquinolones were warranted in children with serious and life-threatening infections. This has been interpreted by the agency to mean that the risk/benefit assessment of the study and consequent use of fluoroquinolones in serious and life-threatening infections is justified at this time.

ANTHRAX:

General Information:

Anthrax is the infection caused by the gram-positive spore-forming rod-shaped bacillus, *Bacillus anthracis*. The organism is found in the soil and in antiquity was a cause of infections in animals and in humans. In the 19th century, occupational anthrax was seen in workers who carded animal wool ("woolsorter's disease"). Today anthrax occurs in some parts of the world but is exceedingly rare because of the use of vaccine in livestock

and high-risk industrial workers. Only a handful of cases have been reported in the US in this century.

Anthrax may be seen in three forms. Cutaneous anthrax is acquired on the skin, generally through cuts of abrasions, by direct contact with infected animals (mortality is estimated 10-20%). Gastrointestinal anthrax results from eating contaminated meat (mortality is high). Inhalational anthrax is transmitted by aerosolized spores of *B. anthracis* which then deposit within the respiratory tract. Mortality from an inhalation anthrax infection is extremely high, estimated as 80-100%. The spores of *B. anthracis* have been produced by some countries as biological warfare. It is also considered likely that *B. anthracis* organisms may be engineered that would be resistant to common antibiotics such as penicillin or the tetracyclines.

Inhalational Anthrax:

Human Disease:

When the spores of *B. anthracis* are inhaled, they deposit in the alveoli, are taken up by pulmonary macrophages and are transported via the pulmonary lymphatic to perihilar and mediastinal lymph nodes. The spores germinate into the vegetative organism. In the vegetative state, the bacillus begins to elaborate the anthrax toxin, comprised of three proteins: the protective antigen (PA), the edema factor (EF) and the lethal factor (LF). The PA protein mediates cell entry of the EF and LF; these interact to cause rapid cellular and host death. As the toxin is released and spreads to the tissues, it causes edema, hemorrhage and necrosis of the infected tissues of the mediastinum, causing mediastinal widening with resultant substernal pain. Hemorrhage and tissue injury can extend to the pleura, affect the trachea causing compression dry cough, stridor. Later in the course, multiple gastrointestinal hemorrhagic lesions and hemorrhagic meningitis develop. Thus, the pathogenesis of the disease caused by *B. anthracis* differs from infections caused by most bacteria that enter the respiratory tract such as *S. pneumoniae, H. influenzae,* etc. The latter bacteria replicate in the pulmonary parenchyma, causing infection and inflammation of the alveoli. In contrast, *B. anthracis* is not typically found within the alveoli, does not elicit an inflammatory response (either in the lungs or other parts of the host) and does not cause a typical pulmonary infection or pneumonia. This difference in pathogenesis accounts for the decisions about initiating antimicrobial use as soon after exposure to the spores as possible and administering drug for 60 days because of continued germination of residual spores (see below).

The Indication - COMMENTS:

The terminology used for this indication, inhalational anthrax (post-exposure), warrants comment.

Inhalational anthrax is a rapidly fatal infection. Once the infection is established, antimicrobial treatment is usually ineffective. Therefore, it would not be appropriate to term the indication as treatment of an infection.

Neither would it be technically correct to refer to the indication as prophylaxis of inhalational anthrax, because prophylaxis means antimicrobials are given before an inciting event, in this case before any exposure to spores occurred. Prophylaxis would not be realistic because of the inability of predicting whether or when such an intentional anthrax exposure will occur.

Thus the indication for approval is termed "INHALATIONAL ANTHRAX (POST-EXPOSURE)" with the further clarification that administration of ciprofloxacin is intended "to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*."

Clinical Course:

The time course of inhalational anthrax is fairly characteristic. The first 1-3 days after exposure, patients may have low-grade fever, malaise, dry cough. To be managed successfully, an exposed person must begin antimicrobial administration within this time period, and most likely within the first 24 hours of exposure.

Following the 1-3 days of nonspecific, "flu-like" symptoms, patients deteriorate rapidly, and develop tachypnea, dyspnea, stridor, high fever, diaphoresis, tachycardia, then hematemesis, melena abdominal pain. Lastly, patients may develop delirium and coma due to meningitis. These changes evolve within the next 1-2 days, and terminate with shock and death. Once the patient starts this rapid downhill course, mortality is almost inevitable and antimicrobials do little to change the course of the disease.

Histology:

As summarized in the application and presented by Dr. David Walker at the July 28, 2000, AntiInfective Advisory Committee meeting, the histopathologic changes of human anthrax are characterized but extensive edema, necrosis and hemorrage of affected tissues, including mediastinal and hilar lymph nodes, the gastrointestinal tract and meninges. Notably, given the respiratory route of entry of the spores and deposition within the alveoli, there were no findings of pulmonary bacterial pneumonia, such as consolidation and inflammation within the pulmonary parenchyma.

In vitro Microbiology:

Review of the microbiology information on 92 clinical and laboratory strains *of B. anthracis* showed the minimum inhibitory concentration (MIC_{90}) of

ciprofloxacin needed to kill 90% of the isolates in vitro is 0.06 mcg/mL. This value is then compared to the attainable peak and trough concentrations of ciprofloxacin in both the human and the monkey, and show that serum concentrations exceed by multiple factors the MIC of the organism. (discussed further below)

SUMMARY OF DATA IN THE SUBMISSION and ADVISORY COMMITTEE MEETING, JULY 28, 2000:

A brief summary of the monkey model submitted to the agency and reviewed at the Advisory Committee is given below.

MACAQUE MONKEY MODEL:

Experiment:

The background, design, results and analysis of the experiment in the rhesus monkey model of inhalational anthrax are found in the primary reviews, the cited literature and the July 28, 2000 Advisory Committee transcript. For purposes of reaching a regulatory decision, two of the 6 arms of the monkey study are relevant: the control group given saline and the experimental group given ciprofloxacin.

Exposure of Monkeys to *Bacillus anthracis*:

In this efficacy study, monkeys were exposed to approximately 12 times the LD50 of spores in a sealed chamber. The spores were introduced into the animals in a manner analogous to the expected exposure in humans, i.e., via aerosol to the respiratory tract. This is noteworthy because many animal models involve introduction of pathogenic organisms in a manner that does not mimic the acquisition of the human disease.

Ciprofloxacin Dosing and Duration in Monkeys:

The monkeys in the experimental arm received ciprofloxacin 125 mg q12h BID for 30 days (following a loading dose of 250 mg). One animal died at day 5 due to a gavage accident. The remaining nine animals survived during the 30 day ciprofloxacin administration period. This is relevant because in the non-primate model, the dosing frequency is comparable to the proposed human regimen.

Drug administration continued for 30 days because previous studies of shorter duration in monkeys and other animals showed that 5, 10 or 20-day regimens were protective while the drugs were administered; however, death followed antimicrobial discontinuation. This pattern is consistent with experimental findings by Henderson showing that spore clearance continues for prolonged periods after exposure.

Time after exposure	% spores retained
42 days	5-20%
50 days	2%
75 days	0.5 – 1%
100 days	trace

Pharmacokinetics of Ciprofloxacin in the Monkeys:

The monkeys in the ciprofloxacin arm had blood samples taken on days 3, 5, 9 and 20 of the study. Both peak and trough levels were assayed. The geometric mean for peak levels ranged from 0.98 – 1.55 mcg/mL for the four sampling days, and the geometric mean for the trough level ranged from 0.11 - 0.18 mcg/mL for these days. These peak and trough levels in the monkeys were similar to or lower than the levels in humans following administration of 500 mg q12h PO, 400 mg q12 IV, and 15 mg/kg PO (children). Furthermore, these ciprofloxacin levels in the monkey were effective in preventing death due to anthrax compared to the saline control arm.

Course of the Disease in Monkeys:

Results of blood cultures from the monkeys were reviewed. Control animals had bacteremia at levels of $10\text{-}10^5$ CFU/mL for about 1-2 days before death due to anthrax. The earliest positive blood culture was seen on day 3 of the study. Nine of ten control animals died of anthrax. Death occurred between day 3 to day 8 following exposure, with a mean time to death of 5.5 days. The one animal that survived had negative cultures.

> **COMMENT:**
> The finding of blood culture positivity within the 1-2 days before death and death an average of 5.5 days after aerosol exposure to *B. anthracis*, shows a clinical time course and outcome strikingly similar to the disease course in humans, as summarized above. These parallel findings further lend support to the use of this model.

In the ciprofloxacin arm, no animal died of anthrax during the 30 days while receiving ciprofloxacin. After ciprofloxacin was stopped, one animal did develop anthrax and died of the disease at day 36 (6 days after ciprofloxacin). There were eight additional animals that survived and were followed for the total 90 days of the study.

Histologic findings of Inhalational Anthrax in the Macaque Monkey Model at Necropsy:

The gross and histologic findings at necropsy included edema, necrosis and hemorrage of various tissues and organs, including mediastinal and hilar lymph nodes, spleen, gastrointestinal tract, meninges as well as the presence of bacilli within various tissues. These findings were presented in the submission and reviewed during the Advisory Committee meeting by Colonel Arthur Friedlander, the principal investigator of the study.

COMMENT:
The gross and histologic changes found in the monkeys which died of inhalational anthrax had a striking similarity to the gross and histological findings reviewed by Dr. Walker from the Sverdlosk experience of human cases of fatal inhalational anthrax. These included the tissues affected (and not affected), the degree and type of injury, and the time course of the disease.

Outcomes in the Monkeys:

Nine of ten control animals died of anthrax and one of nine ciprofloxacin animals died of anthrax. Overall, however, there were 3 of 10 deaths in the ciprofloxacin arm: one due to anthrax at day 36; one due to a gavage accident at day 5; and the third animal died on day 106. This animal had obstructive uropathy, was sacrificed moribund and had no evidence of anthrax at autopsy.

The following table is a summary of the outcome as presented at the July 28, 2000 Advisory Committee meeting.

Intent to Treat Analysis: including all causes of death as failure

Treatment	All Deaths	P vs. control‡	95%[1] CI of ciprofloxacin - control
Control untreated	9/10		
Ciprofloxacin	3/10	0.0198	(-88.7%, -12.3%)

‡ P-value was calculated using a two-tailed Fisher's exact test.
[1] 95% confidence interval was calculated using an exact method.

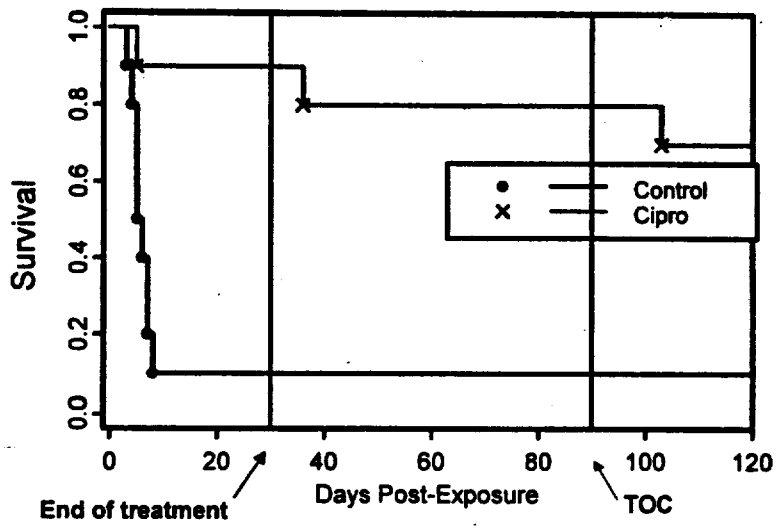
Evaluable Population Analysis: cause of death proven to be due to anthrax

Treatment	Anthrax deaths	P vs. control‡	95%[1] CI of ciprofloxacin – control
Control untreated	9/10		
Ciprofloxacin	1/9	0.0011	(-97.5%, -35.0%)

‡ P-value was calculated using a two-tailed Fisher's exact test.
[1] 95% confidence interval was calculated using an exact method.

APPEARS THIS WAY ON ORIGINAL

Challenge (from Friedlander et al 1993)



COMMENT:
In animals receiving ciprofloxacin, no animal died of anthrax while receiving ciprofloxacin for 30 days. Ciprofloxacin was stopped after 30 days, and one animal died of anthrax on day 36, 6 days after stopping the antimicrobial. This finding indicates that animals are protected from death due to anthrax while receiving antimicrobials. In addition, it shows that not all spores were eliminated from the respiratory tract by 30 days, and some remained, germinated and resulted in clinical disease and death. This observation is relevant in guiding selection of dosing duration.

The Macaque Monkey Model of Inhalational Anthrax – Applicability to the Human disease:

It is noteworthy that there are multiple similarities in this particular animal model to the human disease:

Exposure: The spores gained access to the respiratory tract via an aerosol as would be expected in human inhalational anthrax.

Antimicrobial use: Ciprofloxacin was administered by gavage orally in a q12h regimen for 30 days. The proposed human regimen (oral) is 500 mg q12h for 60 days.

Ciprofloxacin Pharmacokinetics: The 125 mg q12h dose resulted in peak and trough levels that were similar to or somewhat lower than humans ciprofloxacin blood concentrations following 500 mg q12h.

Time course: The time course of the disease – short incubation, rapid down hill course and mortality -- among the animals is similar to a similar time course among people who died of inhalational anthrax in Sverdlosk.

Histopathology: The autopsy findings of inhalational anthrax reported from the Sverdlosk experience and reviewed by Dr. Walker at the Advisory Committee meeting are strikingly similar to the necropsy findings reported by Dr. Friedlander in the monkeys that died of inhalational anthrax.

Ciprofloxacin effectiveness: As reviewed by Drs. Meyerhoff and Dixon, the efficacy of ciprofloxacin compared to placebo (saline) showed a statistically significant difference in favor of antimicrobial administration, whether one looks at the intent to treat analysis (all animals studied) or the per protocol analysis (anthrax deaths).

ADVISORY COMMITTEE RECOMMENDATION:

The members of the advisory committee recommended unanimously (eight of eight) that ciprofloxacin is safe and effective in post-exposure inhalational anthrax and recommended that the duration of ciprofloxacin administration should be 60 days.

REGULATORY CONSIDERATIONS: POLICY ISSUES AND PRECEDENTS:

The Food Drug and Cosmetic Act, Section 505 (d), specifies that drugs should be approved for marketing based on "substantial evidence," defined as,

> ... evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof...

Title 21 of the Code of Federal Regulations, section 314.126 provides information on adequate and well-controlled studies and their role in providing

> ...the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs and antibiotics.

Thus, the expectation is that all drugs/antibiotics are approved based on adequate and well-controlled studies in humans. Inhalational anthrax (post-exposure) is a unique indication and situation. The disease does not occur naturally and to expose people intentionally to the agent and risk any mortality as part of a study is considered unethical.

To study a drug for a highly-fatal biological warfare agent would mean that people would have to be deliberately exposed to the agent, raising an ethical dilemma. This quandry was recognized and a proposed rule was published in the Federal Register on October 5, 1999.

> New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or **Permanently Disabling Toxic** Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted
> AGENCY: Food and Drug Administration, HHS.
> ACTION: Proposed rule
> SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its new drug and biological product regulations to identify the information needed to provide substantial evidence of the efficacy of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. This proposal would apply when the traditional efficacy studies in humans are not feasible and cannot be ethically [[Page 53961]] conducted under FDA's regulations for adequate and well-controlled studies in humans. The agency is proposing this action because it recognizes the need for adequate medical responses to protect or treat individuals exposed to these lethal or **permanently disabling toxic** substances.

The applicability of this proposed rule to these applications was discussed. As elaborated on further below, on further consideration, an alternative approach was used.

In the evaluation of drugs for the treatment of serious and life-threatening diseases (e.g., human immunodeficiency virus (HIV) infections, AIDS, malignancies), drug efficacy has been evaluated on an intermediate or "surrogate" endpoint other than survival or irreversible morbidity. This approach is described under 21 CFR 314.500.
This surrogate endpoint is then confirmed based on definitive or traditional clinical trials in patients.

> Subpart H--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses
> Sec. 314.500 Scope. Source: 57 FR 58958, Dec. 11, 1992, unless otherwise noted.
> This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life- threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).
> [57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]
> Sec. 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
> FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must aiso be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

A critical factor in this consideration is that the surrogate endpoint is considered to reasonably predict the definite or primary endpoint of the study, which in most of these serious and life-threatening diseases is mortality.

In infectious diseases, the causative or etiologic agent is a living organism that can be studied in vitro. The amount of drug needed to kill a microorganism in vitro can be determined and the drug levels achieved in the patients can be measured. Finally, a relationship between the amount of drug needed to kill the organism in a patient must be established. These laboratory parameters may be evaluated as potential surrogate endpoints.

A number of advisory committee meetings have been devoted to the discussion of and consideration of the use of these surrogates (microbiological data, minimum inhibitory concentrations (MIC), drug pharmacokinetics (PK), animal models of infection) in lieu of or in addition to limited clinical data when considering drug approval. At these meetings, the diseases and infecting organisms being considered were ones that occurred naturally and spontaneouly in humans (some rarely) therefore could be studied in adequate and well-controlled studies with clinical endpoints. The recommendation from the advisory committee had been that MIC and PK data should not be used routinely as a sole basis for approval. Further, the committee had recommended that use of a surrogate endpoint should be considered on a case-by-case basis.

The committees in the past had not been asked specifically about the use of a surrogate endpoint when evaluating drug regimens for a biological warfare agent such as the anthrax organism where clinical trials could not be ethically undertaken. Consistent with the recommendation of the case-by-case consideration, the current applications were discussed at the Advisory Committee meeting of July 28, 2000. The committee recommended unanimously that ciprofloxacin for 60 days was a safe and effective regimen for post-exposure inhalational anthrax.

Internal discussions at the agency to address the regulatory basis for the approval of this application included senior staff – Dr. Janet Woodcock, Center Director, Dr. Robert Temple, Associate Director of Policy; Jane Axelard, Regulatory Policy Staff; Dr. Dianne Murphy, Acting Deputy Center Director; Dr. Gary Chikami, Division Director and Coordinator of Bioterrorism activities in ODEIV -- along with staff from the Division of Special Pathogen and Immunologic Drug Products. The various regulatory options were reviewed and the conclusion was reached that the most applicable approach would be to approve this application under 21 CFR 314.510, the Subpart H accelerated approval regulations which allow the agency to rely on a surrogate endpoint.

In this situation, the surrogate endpoint is represented by the ciprofloxacin blood concentrations. The relevance of these concentrations in turn are supported by additional data. First, the peak and trough concentrations of ciprofloxacin in humans have been characterized. Second, these levels substantially exceed (by approximately 30+ fold) the minimum inhibitory concentration (MIC) of the organism, *B. anthracis*. Third, these levels are at least the same as but usually higher than the blood concentrations that were present and documented on multiple days in the monkey model of inhalational anthrax. And finally, in the monkey model, the attained ciprofloxacin concentrations were associated with a statistically significantly superior outcome in preventing death due to

inhalational anthrax (p = .0011). Therefore, it is expected that the proposed human dose will yield blood levels that significantly exceed the MIC of the organism. Ciprofloxacin administration will continue for 60 days, a duration that exceeds the 30 days found effective in the monkey model, and a duration consistent with substantial (>98%) reduction of the inhaled spore load.

SUMMARY RECOMMENDATIONS:

Ciprofloxacin should be approved for the indication of inhalational anthrax (post-exposure).

The dose should be 500 mg q12h for 60 days in adults and 15 mg/kg q12 h for 60 days in pediatric patients. If appropriate, ciprofloxacin may be administered in intravenous form as 400 mg q12h.

Approval of this indication is based on the demonstration that ciprofloxacin is effective in a closely related monkey model, where ciprofloxacin peak and trough levels were above the MIC_{90} of the *Bacillus anthracis,* 0.06 mcg/mL. This information is relevant and provides support for the conclusion that ciprofloxacin blood levels in humans represent levels (surrogate endpoint) that can reasonably be expected to provide clinical benefit by eradicating *B. anthracis* from the human host thus reducing the incidence or progression of disease following exposure to anthrax spores.

However, while this approach may, on the surface, appear applicable to other situations of infectious disease, two factors make this situation unique:

> First, inhalational anthrax (post-exposure) is not encountered as a spontaneous or naturally occurring disease in numbers that could be studied. The mortality of infection is so high that it would be unethical to expose people intentionally to conduct a study. This is in contrast to other infections, which occur naturally and therefore can be studied.
>
> Second, the identification of an experimental animal model in which the disease exposure, disease progression, disease outcome and histopathological findings are virtually parallel to the human disease is uncommon among animal models of infection. The availability of pharmacokinetic information from the actual animals exposed to the anthrax spores and the availability of information on the drug's effectiveness in these animals allows one to determine the effective blood levels. From this, it is possible to extrapolate that levels at or above these effective levels will effectively eradicate the organism, thereby reducing the incidence or reducing the progression of disease due to *B. anthracis.*

Safety data supporting this approval were obtained from the original NDA, from a large data base of post-marketing evidence and from analyses (primarily done by the company) of safety in patients receiving 60 days or longer of ciprofloxacin.

Although fluroquinolones, including ciprofloxacin, are not approved for pediatric use because of arthropathy in weight-bearing joints, documented in juvenile animals, the risk benefit assessment indicates that drug should be administered to children if a post-exposure situation is encountered. Furthermore, the company is conducting an observational study in children to assess the long-term safety, including affects on cartilage.

Finally, no prospective studies in humans can be planned. Instead, Bayer has been asked and agreed to cooperate with U.S.-based public health agencies in evaluating data on the use of ciprofloxacin in a large U.S. population for inhalational anthrax (post-exposure), should an exposure occur.

/S/

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen
and Immunologic Drugs

/S/

Gary Chikami, M.D.
Director, Division of Anti Infective Drug Products
Coordinator, ODE IV Bioterrorism Committee

cc:
NDAs

RECORD OF MEETING

DATE OF MEETING:	August 30, 2000
APPLICATIONS:	NDA 19-537/S-038 NDA 19-847/S-024 NDA 19-857/S-027 NDA 19-858/S-021 NDA 20-780/S-008
DRUG:	CIPRO® (ciprofloxacin)
INDICATION:	Inhalational Anthrax (post – exposure)
SPONSOR:	Bayer Corporation Pharmaceutical Division
SUBJECT:	Promotional Materials
SPONSOR ATTENDEES:	Paul MacCarthy MD, Medical Barbara Painter, Ph.D., Microbiology Andy Verderame, Regulatory Deborah Church, MD, Medical
FDA ATTENDEES:	Renata Albrecht, M.D., Acting Director, DSPIDP Rigoberto Roca, M.D., Medical Team Leader Shukal Bala, Ph.D., Acting Microbiology TL Joette Meyer, Pharm.D., Clin. Pharm. & Biopharm. Reviewer James Rogers, Pharm.D., Reviewer, Div. of Drug Marketing, Advertising and Communications Leah Palmer, R.Ph., Pharm.D., Branch Chief, Div. of Drug Marketing, Advertising and Communications Leo Chan, R.Ph., Project Manager

BACKGROUND:

The six month (priority review) action date for NDA 19-537/S-038 is September 1, 2000 and the six month (priority review) action date for NDA 19-847/S-024, NDA 19-857/S-027, NDA 19-858/S-021, and NDA 20-780/S-008 is September 2, 2000. These applications are being approved under Subpart H regulations (CFR 314.500). Under Subpart H regulations (CFR 314.550), all promotional materials which are intended for dissemination or publication within 120 days following approval, unless

otherwise informed by the agency, must be submitted to the agency for consideration during the preapproval review period. Bayer requests in an electronic correspondence dated August 25, 2000 that the Division of Special Pathogen and Immunologic Drug Products expeditiously review Bayer's press release so that it can be distributed at the time of approval. The Division of Special Pathogen and Immunologic Drug Products and the Division of Drug Marketing, Advertising, and Communications (DDMAC) agree to this request and agree to discuss revisions to this press release on August 30, 2000 while Bayer representatives are here for a meeting concerning another drug product. DDMAC representatives are teleconferenced in for this meeting.

- The Division and DDMAC request the following revisions to the August 25, 2000 press release which Bayer agrees to:
  1) The Division asks that the first sentence in the first paragraph which includes wording regarding CIPRO® being the first antibiotic approved for an indication associated with the intentional use of a lethal biological weapon be revised to include the word "specifically". This sentence subsequently reads as follows: "CIPRO® is the first antibiotic approved specifically for an indication associated with the intentional use of a lethal biological weapon."
  2) The Division objects to the wording in the first sentence, third paragraph regarding CIPRO® being the most widely studied and used fluoroquinolone. This sentence subsequently reads as follows: "Since its introduction in 1987, CIPRO®, made by Bayer Corporation, has been extensively studied and is the most widely used fluoroquinolone antibiotic in the world."
  3) Regarding the last sentence, third paragraph, fourteen (and not eighteen) is the number of approved indications the Agency will allow Bayer to claim in this press release.
  4) On the second page, last paragraph, under Safety Considerations, Bayer is asked to include the phrase "(except for inhalational anthrax post-exposure)". This sentence subsequently reads as follows: "The safety and effectiveness of ciprofloxacin in children, adolescents less than 18 years of age (except for inhalational anthrax post-exposure), pregnant women and lactating women have not been established."

  A facsimile was sent at 14:36 by Bayer which contains the agreed-upon version of Bayer's press release.

- DDMAC representatives ask Bayer if a press packet is planned to be distributed upon approval of these supplements. Bayer states that the press packet they plan to distribute consists of a video, a background fact sheet and reprints of the Morbitiy and Mortality Weekly Report – *Bioterrorism alleging use of anthrax and interim guidelines for management* (Morb Mortal Wkly Rep. 1999;48:69-74.) DDMAC states that these materials will need to be reviewed by DDMAC and the Division before they can be distributed since they are considered promotional materials and are subject to the Subpart H regulations regarding promotional materials. Bayer plans to send by express mail early on August 31, 2000 the

video and asks if the Division will allow distribution of the MMWR reprints. A teleconference is planned with Bayer for August 31, 2000 after the video is received by the Division.

Signature, minutes preparer: /S/ **Date:** 11/7/00

Conference Chair: /S/ **Date:** 11/7/00

Attachment: Electronic correspondence sent by Bayer dated August 25, 2000 which contains draft press release. Final agreed-upon press release dated August 25, 2000 and sent by facsimile at 14:36.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM

DATE: April 13, 2000

TO: Andrew Verderame
Associate Director, Regulatory Affairs

ADDRESS: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(202) 812-5029(fax)

FROM: Valerie Jensen RPh., Project Manager
Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Request for information regarding efficacy supplements submitted to NDAs for Ciprofloxacin for the indication of prophylaxis of Anthrax.

The following information is requested for review of the efficacy supplements for Ciprofloxacin submitted in support of an indication for prophylaxis of Anthrax:

1.) We are requesting submission of the following two references:

Kinzig A, Boivin G, Sorgel F, LeBel M. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Ther 1993;54(4):368-73.

Schaad UB, Abdus Salam M, Aujard Y, et al. Use of fluoroquinolones in pediatrics. Pediatr Infect Dis J 1995;14:1-9.

In addition, we would like the raw data from these studies, if available.

2.) We are requesting information regarding the source of the Rhesus monkeys which were used in the animal study submitted in this application.

Thank-you for your consideration of these requests. Please call Valerie Jensen R.Ph., Project Manager, at (301) 827-2374 with any questions related to this correspondence.

HFD-590/MO/Meyerhoff
HFD-590/Jensen PM
HFD-590/Meyer Clin. Pharm

CC: 19-847/S-024
19-857/S-027
19-858/S-021
19-537/S-038
20-780/S-008
Div. File/HFD-590

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM

DATE: May 12, 2000

TO: Andrew Verderame
Associate Director, Regulatory Affairs

ADDRESS: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(203) 812-5172
(203) 812-5029 (fax)

FROM: Leo Chan RPh., Regulatory Project Manager, for
Valerie Jensen RPh., Regulatory Project Manager

NDA: 19-537/S-038, 20-780/S-008, 19-858/S-021, 19-847/S-024, 19-857/S-027

SUBJECT: Request for Pharmacokinetic Data

1. Please provide the raw pharmacokinetic concentration data (from both phases of the study) obtained from monkeys and discussed in the following article:

   Kelly DJ, Chulay JD, Mikesell P, et al. Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys. JID 1992;166:1184-7.

2. Please resubmit the monkey pharmacokinetic data obtained from Dr. Friedlander's trial:

   "Efficacy of antibiotic treatment and vaccination in protection of rhesus monkeys following aerosol infection with Bacillus anthracis."

   a. The data should be formatted such that the antibiotic concentrations are listed in association with the day and time the sample was obtained.
   b. The relationship tc dose should also be made clear (i.e. peak or trough sample).
   c. Data from each monkey should be listed separately.

If you have any further questions, please contact Valerie Jensen or myself at (301) 827-2127.

Leo Chan, R.Ph., Regulatory Project Manager, for
Valerie Jensen, R.Ph., Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

Bayer

Pharmaceutical
Division

REGULATORY AFFAIRS
400 MORGAN LANE
WEST HAVEN, CT 06516

PHONE (203) 812-5172
FAX (203) 812-5029

FACSIMILE MESSAGE

Date: April 17, 2000

To: Valerie Jensen, Project Manager

From: Andrew S. Verderame

Subject: CIPRO Anthrax submissions

CONFIDENTIAL

Dear Ms. Jensen,

Bayer acknowledges receipt of a facsimile message on April 13, 2000 concerning the Anthrax supplements. Bayer had submitted these supplements on February 29, 2000 to all CIPRO New Drug Applications.

Find attached the two references requested. Bayer will also formally submit these articles as a Response to a Request for Information to the NDAs. We are presently determining whether any raw data can be provided. In addition, a Bayer representative will be contacting Dr. Friedlander regarding the source of the rhesus monkeys used in his study.

I will forward additional information to you as soon as possible. If there are any questions or if I can provide any further information, please contact me at (203) 812-5172.

Sincerely,

Andrew S. Verderame
Associate Director, Regulatory Affairs

Memorandum

Date: August 28, 2000

To: **NDA 19-537** CIPRO (ciprofloxacin hydrochloride tablets, 100, 250, 500, and 750 mg)
NDA 19-847 CIPRO IV (ciprofloxacin, 1% solution vials; 200 and 400 mg)
NDA 19-857 CIPRO IV (ciprofloxacin, 0.2% in 5% dextrose; 200 and 400 mg)
NDA 19-858 CIPRO IV (ciprofloxacin, 0.2% in 0.9% sodium chloride; 200 and 400 mg)
NDA 20-780 CIPRO (ciprofloxacin oral suspension; 5g and 10g per 100mL)

From: Dorota Matecka, Ph.D., Chemistry Reviewer, HFD-830/590

Through: Norman Schmuff, Ph.D., Chemistry Team Leader, HFD-590 /S/ 8/29/00

Re: **Environmental Assessment** (exemption request provided in the 6/20/00 amendment to the following supplements: **NDA 19-537/S-038, NDA 19-847/S-024, NDA 19-857/S-027, NDA 19-858/S-021, and NDA 20-780/S-008)**

The above efficacy supplements submitted on February 29, 2000 provide for a new indication for ciprofloxacin, prophylaxis for inhalation anthrax exposure.

Ciprofloxacin is a fluoroquinolone approved for use as a broad-spectrum antibacterial agent. The approved uses for the tablet, oral suspension, and IV forms include: acute sinusitis, lower respiratory tract infections, acute exacerbation of chronic bronchitis, urinary tract infection, acute uncomplicated cystitis, chronic bacteria prostatitis, complicated intra-abdominal infections, skin and akin-structure infections, bone and joint infections, infectious diarrhea, typhoid fever, and uncomplicated cervical and urethral gonorrhea. The current supplements provide for a new indication for ciprofloxacin.

These efficacy supplements do not require a Chemistry Manufacturing and Control (CMC) review because no CMC changes were made within these submissions. The only pertinent item to the CMC review in these efficacy supplements is the EA (environmental assessment).

However, the applicant (Bayer Corporation Pharmaceutical Division) has submitted an amendment dated June 20, 2000 requesting an exemption of an environmental assessment for these submissions.

The applicant stated that since there would be no significant increase in production ~~or use~~ of ciprofloxacin, therefore, as per CFR section 25.31(a), the submission of an environmental assessment is not required. The request is acceptable.

cc:
NDA 19-537/S-038, 19-847/S-024, 19-857/S-027, 19-858/S-021, and 20-780/S-008 (2 copies)
HFD-590/Division File
HFD-590/PM/VJansen
HFD-590/Chem/DMatecka
HFD-590/TL/NSchmuff

HFDS90
FRITSCH

DEPARTMENT OF HEALTH & HUMAN SERVICES · Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: June 14, 2000

TO: Andrew Verderame,
Associate Director, Regulatory Affairs

ADDRESS: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(203) 812-5172
(203) 812-5029 (fax)

FROM: Jeff Fritsch, R.Ph., Regulatory Project Manager

NDAs: 19-537/S-038, 19-847/S-024, 19-857/S-027, 19-858/S-021, and 20-780/S-008

SUBJECT: Request for information regarding efficacy supplements for ciprofloxacin submitted in support of an indication for prophylaxis of Anthrax.

Due to the priority of this review, we would appreciate it if the sponsor could provide the following Information on the human pharmacokinetics of ciprofloxacin:

1. Please provide the steady state peak and trough concentrations (mean and range) in males and females obtained with administration of a 500mg dosing regimen.
2. Please provide the time to reach steady state concentrations. The data requested in items 1 and 2 may be from in-house data as well as data from the literature.
3. Please provide information regarding the penetration of ciprofloxacin into lymph node tissue. Also, if available, please provide human data.
4. Finally, the Division understands that the sponsor will be making a presentation at the upcoming Advisory Committee Meeting. When available, please share with the Division the information on the pharmacokinetics of ciprofloxacin that will be presented.

If you have any questions, please do not hesitate to contact me at (301) 827-2371.

/S/

Jeff Fritsch, R.Ph., Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Product

RECORD OF TELECONFERENCE

DATE OF TELECONFERENCE: August 31, 2000

APPLICATIONS:
NDA 19-537/S-038
NDA 19-847/S-024
NDA 19-857/S-027
NDA 19-858/S-021
NDA 20-780/S-008

DRUG: CIPRO® (ciprofloxacin)

INDICATION: Inhalational Anthrax (post – exposure)

SPONSOR:
Bayer Corporation
Pharmaceutical Division

SUBJECT: Promotional Materials

SPONSOR ATTENDEES:
Paul MacCarthy MD, Medical
Barbara Painter Ph.D., Microbiology
Andy Verderame, Regulatory
Deborah Church MD, Medical
Keith Abrams, Legal
Edward Huegenel, Ph.D., Project Manager

FDA ATTENDEES:
Renata Albrecht, M.D., Acting Director, DSPIDP
Gary Chikami, M.D., Director, Division of Anti-Infective Drug Products
Rigoberto Roca, M.D., Medical Team Leader
Andrea Meyerhoff, M.D., Medical Reviewer
James Rogers, Pharm.D., Reviewer, Div. of Drug Marketing, Advertising and Communications
Leah Palmer, R.Ph., Pharm.D., Branch Chief, Div. of Drug Marketing, Advertising and Communications
Ellen Frank, R.Ph., CPMS
Leo Chan, R.Ph., Project Manager
Valerie Jensen, R.Ph., Project Manager

BACKGROUND:
The six month (priority review) action date for NDA 19-537/S-038 is September 1, 2000 and the six month (priority review) action date for NDA 19-847/S-024, NDA 19-857/S-027, NDA 19-858/S-021, and

NDA 20-780/S-008 is September 2, 2000. These applications are being approved under Subpart H regulations (CFR 314.500). Under Subpart H regulations (CFR 314.550), all promotional materials which are intended for dissemination or publication within 120 days following approval, unless otherwise informed by the agency, must be submitted to the agency for consideration during the preapproval review period. Bayer requested in an electronic correspondence dated August 25, 2000 that the Division of Special Pathogen and Immunologic Drug Products expeditiously review Bayer's press release so that it could be distributed at the time of approval. The Division of Special Pathogen and Immunologic Drug Products and the Division of Drug Marketing , Advertising and Communications (DDMAC) agreed to discuss revisions to this press release on August 30, 2000 while Bayer representatives were here for a meeting concerning another drug product. During the August 30, 2000 meeting, Bayer was asked about whether a press packet would be distributed upon approval of these supplements. Bayer stated that a press packet was planned to be distributed upon approval. DDMAC informed Bayer that the press packet would need to be reviewed by the Division and by DDMAC before it could be distributed since the press packet is considered to be promotional material. Bayer sent the video included with the press packet to the Division on August 31, 2000 and a teleconference was scheduled with Bayer and DDMAC after the video was received and reviewed.

- The video Bayer sent to the Division includes footage from an interview with Dr. John Bartlett,an infectious disease specialist, footage of emergency personnel responding to a potential anthrax exposure incident, and a clip of a production line during the manufacturing process for CIPRO®. Text on the screen is also provided. This video is planned for distribution to news agencies to be used along with a newscaster's coverage of the approval of these supplements. The Division and DDMAC state the following:

  1) Since this material was received immediately prior to the action dates for these supplements, the Division and DDMAC have not had sufficient time to review the video and other materials. The Division and DDMAC agree that Bayer can use only the manufacturing site footage in a video at the time of approval but no other footage may be included unless the Agency has adequate time for review. The text on this video may only include wording from the final version of the Press Release which was discussed and agreed upon on August 30, 2000 and was sent by facsimile at 14:36. Distribution by Bayer of the MMWR *Bioterrorism alleging use of anthrax and interim guidelines for management,* (Morb Mortal Wkly Rep. 1999;48:69-74) will be allowed.

  2) Any additional materials that Bayer would like to use for promotion regarding the indication of inhalational anthrax (post exposure) will need to be reviewed by DDMAC and the Division before these materials can be distributed (per the Subpart H regulations (CFR 314.550)).

Signature, minutes preparer: /S/ **Date:** 11/8/00

Conference Chair: /S/ **Date:** 11/8/00