CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-805

MICROBIOLOGY REVIEW(S)

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Division of Anti-Infective Drug Products
Clinical Microbiological Review

NDA #: 20-805 **MICRO.REVIEW #:** 1 **REVIEW DATE:** 08-MAY-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	07-FEB-97	10-FEB-97	24-MAR-97

NAME & ADDRESS OF APPLICANT: Bayer Corporation Pharmaceutical Division
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DRUG PRODUCT NAME

Proprietary:	CIPRO® HC OTIC Suspension
Nonproprietary/USAN:	ciprofloxacin Otic suspension
Code Names/#'s:	
Chemical Type/	Fluoroquinolone
Therapeutic Class:	3S

ANDA Suitability Petition/DESI/Patent Status:
U.S. Patent No. 4,670,444–expiration date: 12/9/2003 for drug, drug prpduct, method of use. Owned by Bayer Aktiengesellschaft.

U.S. Patent No. 4,844,902–expiration date: 2/11/2008 for drug product. Owned by Bayer Aktiengesellschaft.

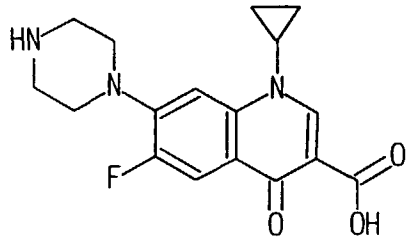
PHARMACOLOGICAL CATEGORY/INDICATION:
Fluoroquinolone/acute diffuse bacterial external otitis

DOSAGE FORM:	Suspension
STRENGTHS:	0.2%(2 mg/mL)
ROUTE OF ADMINISTRATION:	Otic
DISPENSED:	X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

Structure:



Molecular Formula: $C_{17}H_{18}FN_3O_3$
Molecule Weight: 331.4

SUPPORTING DOCUMENTS:
NDA 19-874--Cipro IV 1% solution vials
NDA 19-537--Ciprofloxacin HCl Tablets

RELATED DOCUMENTS (if applicable):
IND

CONSULTS: NONE

REMARKS/COMMENTS:
This application is for the use of ciprofloxacin hydrochloride, a fluoroquinolone with activity against both gram-negative and gram-positive bacteria combined with the anti-inflammatory corticosteroid, hydrocortisone, for the treatment of acute diffuse bacterial external otitis.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY section of the package insert. These revisions are listed as notification to the sponsor at the end of this review on pages 21-22.

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INTRODUCTION

This application is for CIPRO HC Otic Suspension which contains ciprofloxacin hydrochloride combined with the anti-inflammatory corticosteroid, hydrocortisone, in a suspension for otic use. Each milliliter contains ciprofloxacin hydrochloride equivalent to 2 milligrams of ciprofloxacin, 10 milligrams of hydrocortisone, and 9 milligrams of benzyl alcohol as a preservative.

The product is intended for the treatment of acute diffuse bacterial external otitis caused by organisms susceptible to ciprofloxacin, including *Pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter anitratus (baumannii), Proteus mirabilis, Stenotrophomonas maltophilia* and *Enterococcus faecalis*.

Acute diffuse external otitis is most commonly bacterial in origin, but the diagnosis is clinical and the treatment is empirical. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the two most commonly implicated bacterial causes.

Two controlled, multi-center trials were performed and included in this submission. In both trials (one in the United States and one in Europe) ciprofloxacin otic suspension was compared to polymyxin B sulfate-neomycin sulfate-hydrocortisone suspension.

PRECLINICAL EFFICACY (*In Vitro*)

Mechanism of Action

No new information has been provided. Ciprofloxacin, like the other quinolones, exerts its antibacterial activity by entering the bacterial cell and interacting with bacterial DNA gyrase. This interaction results in interference with the vital supercoiling of the DNA, and inhibits DNA synthesis.

Antimicrobial Spectrum of Activity

The *in vitro* activity of ciprofloxacin was presented in NDA 19-537 for ciprofloxacin tablets. More recent data, demonstrating the activity of ciprofloxacin against bacteria that may be associated with ear infections were collected in a national surveillance study conducted by International Health Management Associates (IHMA) during the year 1994. Approximately 150 demographically diverse institutions are in the study. The designations Susceptible ($\leq$ 1.0 μg/mL), Intermediate (2.0 μg/mL), and Resistant ($\geq$ 4.0 μg/mL) used in this IHMA study are based on pharmacokinetic properties of ciprofloxacin in systemic infections

and are not applicable to topically administered drug. These breakpoints are the ones in the label for ciprofloxacin tablets and parenteral formulations. The concentration of 0.2% ciprofloxacin in the otic preparations in this submission are higher than those found in serum. About 300 μg (3 drops= 0.15 mL of a 2000 μg/mL suspension) of the drug is delivered in each dose of the otic preparation.

Nonfermentative Gram-Negative Rods

TABLE 1 shows the ciprofloxacin surveillance data collected in 1994 by for nonfermentative gram-negative rods.

TABLE 1
Ciprofloxacin Surveillance Data for Nonfermentative Gram-Negative Rods

Organism	Susceptible %	Intermediate %	Resistant %	No. Tested
Pseudomonas aeruginosa	79.0	3.6	17.4	55,593
Acinetobacter anitratus	78.9	1.5	19.6	1397
Acinetobacter lwoffi	88.9	1.6	9.5	1203
Stenotrophomonas maltophilia	30.5	25.6	43.9	1683

Surveillance Data collected by
Annual Antimicrobial Surveillance Database--1994

The above data show that about 80% of *Pseudomonas aeruginosa* isolates are susceptible at a ciprofloxacin concentration of ≤ 1 μg/mL. *Acinetobacter anitratus* isolates show similar *in vitro* susceptibility. Most strains of *Stenotrophomonas maltophilia* are not susceptible to ciprofloxacin. These percentages, however, are based on systemic breakpoints and are not appropriate for this product. Since a higher concentration is available at the site of infection when the drug is applied topically, the percentage of isolates susceptible to this drug product would be expected to be higher than those indicated in the above table.

Gram-Positive Cocci

TABLE 2 shows the ciprofloxacin surveillance data collected in 1994 by for gram-positive cocci.

TABLE 2
Ciprofloxacin Surveillance Data for Gram-Positive Cocci

Organism	Susceptible %	Intermediate %	Resistant %	No. Tested
Enterococcus faecalis	63.4	9.7	26.9	11292
Staphylococcus aureus[a]	78.4	1.9	19.7	92045
Streptococcus pyogenes	87.2	9.0	3.8	524
Staphylococcus epidermidis[b]	61.0	1.7	37.3	18373

Surveillance Data collected by
Annual Antimicrobial Surveillance Database--1994
[a] Includes methicillin resistant and susceptible isolates. Methicillin resistance was at 19.5%.
[b] Includes methicillin resistant and susceptible isolates. Methicillin resistance was at 62.7%.

The above data show that about 60% of *Enterococcus faecalis* isolates are susceptible at a ciprofloxacin concentration of ≤ 1 μg/mL. The above table combines methicillin-susceptible and methicillin-resistant strains of staphylococci. This lowers the percentage that are susceptible. In another study that differentiated these strains, the MIC_{90} for 367 strains of methicillin-susceptible *Staphylococcus aureus* was 0.5 μg/mL compared to an MIC_{90} of > 8 μg/mL for methicillin-resistant *Staphylococcus aureus*. About 90% of the *Streptococcus pyogenes* isolates were susceptible to ciprofloxacin. These percentages, however, are based on systemic breakpoints and are not appropriate for this product. Since a higher concentration is available at the site of infection when the drug is applied topically, the percentage of isolates susceptible to this drug product would be expected to be higher than those indicated in the above table.

Enterobacteriaceae

TABLE 3 shows the ciprofloxacin surveillance data collected in 1994 by for Enterobacteriaceae.

TABLE 3
Ciprofloxacin Surveillance Data for Enterobacteriaceae

Organism	Susceptible %	Intermediate %	Resistant %	No. Tested
Citrobacter diversus	98.0	0.7	1.3	2906
Citrobacter freundii	90.9	2.0	7.1	5831
Enterobacter aerogenes	95.1	0.7	4.2	7205
Enterobacter cloacae	95.1	1.0	3.9	14527
Escherichia coli	99.3	0.1	0.6	124326
Klebsiella oxytoca	95.6	1.0	3.4	5682
Klebsiella pneumoniae	95.5	0.9	3.6	31817
Morganella morganii	93.1	0.7	6.2	3488
Proteus mirabilis	95.0	1.0	4.0	19180
Proteus vulgaris	98.6	0.3	1.1	1186
Providencia rettgeri	89.8	1.9	8.3	679
Providencia stuartii	55.0	4.7	40.3	1661
Serratia marcescens	87.4	4.0	8.6	6792

Surveillance Data collected by
Annual Antimicrobial Surveillance Database--1994

The above data show that ciprofloxacin is active against most *Enterobacteriaceae*. With the exception of *Providencia stuartii*, most clinical isolates of this group are inhibited *in vitro* by concentrations of ≤ 1.0 μg/mL. Only 55% of the *Providencia stuartii* isolates were susceptible, while all other tested species had over 85% susceptible at this concentration.

Primary Respiratory Tract Pathogens

Susceptibility data for primary pathogens of respiratory tract infections are shown in TABLE 4.

TABLE 4
Susceptibility of Primary Respiratory Tract Pathogens[a]

Organism	Ref	No.	MIC_{50}	MIC_{90}	% Susceptible	% Resistant
Streptococcus pneumoniae	1	1078	NG[b]	NG	90	4
	2	99	1	2	82	NG
	3	404	0.5	1	98	0.7
Haemophilus influenzae	2	94	≤0.008	0.015	100	0
	3	330	≤0.03	0.03	99.7 (≤0.03)	NG
Moraxella catarrhalis	1	142	NG	NG	100	0
	3	250	0.008	0.015	100 (≤0.03)	0

[a] All organisms were isolated from multicenter studies in 1994.
[b] Not Given

The surveillance study (1) demonstrated that 90% of the 1,078 isolates of *Streptococcus pneumoniae* were inhibited by ≤ 1.0 μg/mL ciprofloxacin. The data from the other two studies (2,3) were similar, although the MIC_{90} value in study (2) which tested only 99 isolates was 2.0 μg/mL. These data are similar to those from the NDA for ciprofloxacin tablets.

Haemophilus influenzae and *Moraxella catarrhalis* all had very low MIC values (usually ≤0.03 μg/mL). These MIC values are similar to those reported in the NDA for ciprofloxacin tablets.

All these data demonstrate that ciprofloxacin has significant *in vitro* activity against the organisms most often associated with otitis externa including *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus aureus*, and *Enterobacteriaceae* even at the systemic susceptible breakpoint of ≤ 1.0 μg/mL. The *in vitro* activity against *Enterococcus faecalis* and *Stenotrophomonas maltophilia* is not as good, especially for *S. maltophilia* isolates (only about 30% susceptible at ≤ 1.0 μg/mL). Based on the dose of 3 drops (0.15 mL) which contains 300 μg of ciprofloxacin, the *in vitro* activity of ciprofloxacin should be even better.

Mechanism of Resistance Studies

No new information has been included in this submission. Studies submitted in the NDA for ciprofloxacin tablets showed the frequency of spontaneously occurring mutants resistant to ciprofloxacin is rare. Spontaneous single-step resistance frequencies are usually 10^{-9} to 10^{-11}. Mutation frequencies for *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* are higher at rates of 10^{-6} to 10^{-7}.

Multistep resistance following serial transfer in subinhibitory concentrations of ciprofloxacin does develop after 10 to 20 transfers. This phenomenon is generally seen more with *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*.

Most resistance develops due to a change in the DNA that codes for the gyrase enzyme. Most mutations are in the *gryA* gene that codes for the A-subunit of the gyrase. A *norA* gene has also been found in some gram-positive bacteria. This gene produces a protein that appears to mediate norfloxacin and some other quinolone efflux.

Epidemiological Studies

Ciprofloxacin hydrochloride-hydrocortisone otic suspension has not been marketed in any country. No marketing applications are pending in any country. Applications are expected to be filed in 1997. There is, therefore, no epidemiological information to report.

PRECLINICAL EFFICACY (*IN VIVO*)

Pharmacokinetics/Bioavailability

This product is for topical application. No new pharmacokinetic studies were performed. It is predicted that the administration of this ciprofloxacin otic preparation in doses proposed for clinical trials will result in systemic ciprofloxacin concentrations below the detection limits.

A single 3-drop dose of ciprofloxacin otic delivers approximately 300 μg of drug. This amount should exceed the MIC_{90} of all relevant pathogens associated with acute otitis externa.

Animal Prophylactic and Therapeutic Studies

In addition to previous animal studies, submitted in the application for ciprofloxacin tablets, a monkey animal model of chronic suppurative otitis media is submitted in this application (4).

Each of four groups of ten cynomolgus monkeys was treated ototopically twice daily with saline, vehicle alone, cortisporin, or 0.2% ciprofloxacin plus vehicle, respectively. The right tympanic membrane of each monkey was perforated and then challenged with up to 10^5 CFU of *Pseudomonas aeruginosa* strain ATCC 27853. The ears were allowed to drain for 3 weeks before the onset of 4 weeks of treatment.

Ears were examined twice weekly, at 3-4 day intervals. At the time of each examination, the external ear canal was cleaned of debris and a sterile calcium alginate swab was inserted directly into the middle ear through the existing perforation. If the tympanic membrane was healed, a new perforation was made under sterile conditions, and any existing effusion was cultured. For each sample, the swab was streaked immediately onto chocolate agar plates (for isolation of any bacteria present) and then onto pseudocel plates (to select for *P. aeruginosa*). *Pseudomonas aeruginosa* and other bacterial species were identified and their relative abundances recorded at each time point by a microbiologist blinded to group assignment of the animals. Ciprofloxacin sensitivities of randomly selected *P. aeruginosa* colonies as well as those of other organisms were evaluated.

After 3 weeks of treatment, all ears in the ciprofloxacin and cortisporin groups were negative for *Pseudomonas*. In contrast, 8 or the ears in the saline treatment group were still culture positive for *Pseudomonas* at the end of the study. The vehicle treatment group had a cure rate with respect to *Pseudomonas* elimination intermediate between those of the saline and ciprofloxacin groups.

Overall, a total of 272 samples grew *Pseudomonas* and 129 of these were evaluated for susceptibility to ciprofloxacin. All of the 129 samples were rated as susceptible.

This study shows that in this model ciprofloxacin works as well as cortisporin against *Pseudomonas aeruginosa* and is better than saline and vehicle alone.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS

The sponsor has presented two phase III studies for the treatment of acute diffuse bacterial external otitis. The dosage for this indication is three drops twice daily for seven days.

STUDY D94-008-- Randomized, non-blinded, multicenter, controlled efficacy study of ciprofloxacin otic drops with or without hydrocortisone versus polymyxin B-neomycin-hydrocortisone otic drops in the treatment of acute diffuse bacterial external otitis.

STUDY SN1439-- Randomized, non-blinded, multicenter, controlled efficacy study of ciprofloxacin otic drops with or without hydrocortisone versus polymyxin B-neomycin-hydrocortisone otic drops in the treatment of acute diffuse bacterial external otitis.

Study D94-008 was performed in the United States and study SN1439 was performed in Europe. In each study there were three treatment groups: ciprofloxacin otic solution (CIP-SOLN) , ciprofloxacin otic suspension with hydrocortisone (CIP-HC-SUSP), and polymyxin B-neomycin-hydrocortisone (PNH). For both trials there was one visit during treatment (day 2-3) if clinical symptoms were not improved, and two post-treatment visits (3-7 and 14-28 days post) following the end of treatment.

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ON ORIGINAL

USA STUDY D94-008

A total of 228 organisms were isolated from 161 patients in the ciprofloxacin solution group, 217 organisms from 156 patients in the ciprofloxacin suspension group, and 210 organisms from 151 patients in the polymyxin B-neomycin group. A total of 417 organisms in the ciprofloxacin groups were evaluable for bacteriological response. TABLE 5 shows the overall bacteriological response. Organisms were "presumed eradicated" if there were inadequate specimen to culture at the end of therapy. Bacteriological eradication by patient at end of therapy, was 93% in the CIP-SOLN, 95% in the CIP-HC-SUSP, and 88% in the PNH treatment group.

Bacterial superinfections in the ear canal were reported for 30 patients (13 CIP-SOLN, 6 CIP-HC-SUSP, 11 PNH). In the CIP-SOLN group, the organisms causing superinfection included *Klebsiella pneumoniae* (n=1), *Staphylococcus aureus* (n=2), *Enterobacter* species (n=1), *Achromobacter* species (n=2), *Acinetobacter* species (n=3), *Flavobacterium* species (n=1), *Pasteurella multocida* (n=1), and *Pseudomonas* species (n=2). Superinfections in the CIP-HC-SUSP treatment group were *Stenotrophomonas maltophilia* (n=1), *Pseudomonas* species (n=1), *Achromobacter* species (n=1), and *Acinetobacter* species (n=4). In the PNH group superinfecting pathogens included *Klebsiella oxytoca* (n=2), *Staphylococcus aureus* (n=1), *Aeromonas hydrophilia* (n=2), *Acinetobacter* species (n=6), *Flavobacterium* species (n=1), *Pseudomonas* species (n=3), and *Streptococcus* species (n=1).

At the follow-up visit a total of 11 organisms were associated with recurrence of reinfection. Reinfections were due to *Proteus mirabilis* (1-PNH), *Stenotrophomonas maltophilia* (1 in each of the three treatment groups), *S. aureus* (1-CIP-SOLN), and *Alcaligenes* species (1-CIP-HC-SUSP). Recurrences were caused by *S. aureus* (2-CIP-HC-SUSP), *P. aeruginosa* (1-CIP-SOLN, 1-PNH), and *Enterobacter aerogenes* (1-PNH).

It appears that superinfections, reinfections, and recurrences were about equal between the ciprofloxacin treated groups and the control group.

TABLE 5

Bacteriological Response by Organism at End of Treatment (US)

	Eradication/Total (% Erad)
	CIP-SOLN
P. aeruginosa	143/145 (99)
S. aureus	13/13 (100)
S. maltophilia	5/6 (83)
A. anitratus	6/6 (100)
Other	46/46 (100)
	CIP-HC-SUSP
P. aeruginosa	132/134 (99)
S. aureus	16/17 (94)
S. maltophilia	5/5 (100)
A. anitratus	9/9 (100)
Other	37/37 (100)
	PNH
P. aeruginosa	125/136 (92)
S. aureus	12/12 (100)
S. maltophilia	8/8 (100)
A. anitratus	5/6 (83)
E. aerogenes	6/7 (86)
Other	34/35 (97)

Other organisms in the ciprofloxacin treated groups include: *Proteus mirabilis* (10), *Enterobacter cloacae* (8), *Enterobacter aerogenes* (7), *Klebsiella pneumoniae* (6), *Klebsiella* species (7), *Escherichia coli* (5).

Overall bacterial eradication by organism at the end of therapy was 99%, 99%, and 93% for the CIP-SOLN, CIP-HC-SUSP, and the PNH group, respectively. Three organisms in the CIP-SOLN group (2 *Pseudomonas aeruginosa,* and 1 *Stenotrophomonas maltophilia*), three organisms in the CIP-HC-SUSP group (2 *Pseudomonas aeruginosa*, 1 *Staphylococcus aureus*) and 14 organisms in the PNH group (11 *Pseudomonas aeruginosa*, and one each of *A. anitratus, E. aerogenes*, and *Proteus mirabilis*) persisted at the end of therapy. It appears the bacteriological eradication was better in the ciprofloxacin treated groups than in the control group.

The frequency of MICs and the corresponding bacteriological response for the organisms isolated most often during the USA study are listed in TABLE 6.

TABLE 6
Frequency of MICs for Predominant Organisms Isolated in USA

Organism	MIC (μg/mL)							
	≤ 0.5		1.0		2.0		≥4.0	
	E	P	E	P	E	P	E	P
P. aeruginosa (279)	273	4	-	-	1	-	1	-
S. aureus (30)	29	1	-	-	-	-	-	-
S. maltophilia (12)	1	-	2	-	4	1	4	-
A. baumannii (anitratus)	15	-	-	-	-	-	-	-
Enterobacteriaceae (57)	57	-	-	-	-	-	-	-

E=Eradication; P=Persistence

The above table shows that the 4 persistent isolates of *Pseudomonas aeruginosa* had MICs of ≤0.5 μg/mL. The 4 isolates of *Stenotrophomonas maltophilia* that had MICs of ≥4.0 μg/mL were eradicated. This indicates that bacteriological response was not related to MICs. TABLE 7 shows the bacteriological response of organisms with MICs > 0.5 μg/mL in the USA study. As can be seen almost all of these pathogens were eradicated even the ones with an MIC ≥ 4.0 μg/mL. This indicates that systemic breakpoints do not indicate bacteriological success rates for this topical otic product.

TABLE 7
Bacteriological Response for Organisms with MIC >0.5 μg/mL in USA

Organism	MIC (μg/mL)		
	1.0	2.0	≥ 4.0
Stenotrophomonas maltophilia	2 (E)	4 (E), 1 (P)	4 (E)
Pseudomonas aeruginosa		1 (E)	1 (E)
Weeksella species		1 (E)	
Enterobacter aerogenes	1 (E)		
Streptococcus group B	1 (E)		
Alcaligenes species			2 (E)
Achromobacter xylosoxidans		1 (E)	
Total	4 (E)	7 (E), 1 (P)	7 (E)

A summary of the clinical response of the predominant otitis externa organisms isolated during the USA clinical trial is shown in TABLE 8. Clinical resolution or improvement occurred for 91% of *Pseudomonas aeruginosa*, 90% of

Staphylococcus aureus, 94% of *Acinetobacter (anitratus) baumannii*, 93% of *Stenotrophomonas maltophilia*, and 82% of the *Enterobacteriaceae*. The overall failure rate was 11%.

TABLE 8
Clinical Response by Predominant Organisms in USA Study

Organism (No.)	Resolution		Improvement		Failure	
	No.	%	No.	%	No.	%
Pseudomonas aeruginosa (294)	224	(76)	44	(15)	26	(9)
Staphylococcus aureus (31)	23	(74)	5	(16)	3	(10)
Acinetobacter anitratus (16)	13	(81)	2	(13)	1	(6)
Stenotrophomonas maltophilia (14)	9	(64)	4	(29)	1	(7)
Enterobacteriaceae (62)	35	(56)	16	(26)	11	(18)
All organisms (441)	317	(72)	77	(17)	47	(11)

EUROPEAN STUDY SN 1439

A total of 503 bacterial causative organisms were isolated at pretreatment (161 CIP-SOLN, 196 CIP-HC-SUSP, 146 PNH) from 341 patients. The most common organisms was *Pseudomonas aeruginosa*, which was isolated from 81% of patients with a pretreatment organism. TABLE 9 lists the most frequently isolates organisms by treatment and their rate of eradication. Bacteriological eradication by patient at end of therapy, was 88% in the CIP-SOLN, 84% in the CIP-HC-SUSP, and 74% in the PNH treatment group.

Bacterial superinfections in the ear canal were reported for 16 patients (5 CIP-SOLN, 6 CIP-HC-SUSP, 5 PNH). In the CIP-SOLN group, the organisms causing superinfection included *Pseudomonas aeruginosa* (n=5), *Staphylococcus aureus* (n=4), and *Proteus mirabilis* (n=1). Superinfections in the CIP-HC-SUSP treatment group included *Clostridium* species (n=2), *Enterococcus faecalis* (n=1), *Pseudomonas aeruginosa* (n=2), *Staphylococcus aureus* (n=2), and *Stenotrophomonas maltophilia* (n=1). In the PNH group superinfecting pathogens included *Pseudomonas aeruginosa* (n=5), *Staphylococcus aureus* (n=1), *Enterococcus* species (n=1), beta hemolytic streptococci group B (n=1), and *Enterococcus faecalis* (n=1). The number of superinfections is about equal in each treatment group.

At the follow-up visit a total of 5 organisms were associated with reinfection. Reinfections were due to one organism each of *Bacteroides fragilis*, *Bacteroides* species, *Candida* species, *Clostridium perfringens*, and *Pseudomonas aeruginosa*. There were no recurrences in any of the treatment groups.

TABLE 9
Bacteriological Response by Organism at End of Treatment
(Europe)

	Eradication/Total (% Erad)
	CIP-SOLN
P. aeruginosa	86/95 (91)
S. aureus	19/19 (100)
E. faecalis	10/10 (100)
Other	25/25 (100)
	CIP-HC-SUSP
P. aeruginosa	98/109 (88)
S. aureus	22/25 (88)
E. faecalis	11/12 (92)
Other	32/32 (100)
	PNH
P. aeruginosa	74/96 (77)
S. aureus	15/16 (94)
Other	23/24 (96)

Other organisms in the ciprofloxacin treated groups include: *Proteus mirabilis* (8), *Escherichia coli* (3), *Klebsiella oxytoca* (4), *Serratia marcescens* (1).

Overall bacterial eradication by organism at the end of therapy was 94 for CIP-SOLN, 91% for CIP-HC-SUSP, and 82% for PNH. Nine organisms in the CIP-SOLN (all *Pseudomonas aeruginosa*), 17 in the CIP-HC-SUSP group (11 *Pseudomonas aeruginosa*, 3 *Staphylococcus aureus*, and one each of *A. niger, Aspergillus* species, and *Enterococcus faecalis*), and 24 organisms in the PNH treatment group (22 *Pseudomonas aeruginosa*, and one each of *Staphylococcus aureus,* and *Enterococcus faecalis*) persisted at the end of therapy. Eradication rates for the ciprofloxacin treated groups appear to be slightly higher than for the control group. The bacteriological eradication rates in this European study also appear to be lower than in the USA study.

The frequency of MICs and the corresponding bacteriological response for the organisms isolated most often during the European study are listed in TABLE 10.

TABLE 10
Frequency of MICs for Predominant Organisms Isolated in European Study

Organism	MIC (μg/mL)							
	≤ 0.5		1.0		2.0		≥4.0	
	E	P	E	P	E	P	E	P
P. aeruginosa (204)	177	17	6	1	1	-	-	2
S. aureus (44)	40	3	1	-	-	-	-	-
E. faecalis (22)	10	-	9	-	1	-	1	1
Enterobacteriaceae (16)	16	-	-	-	-	-	-	-

E=Eradication; P=Persistence

The above table shows that 17/20 of the persistent isolates of *Pseudomonas aeruginosa* had MICs of ≤0.5 μg/mL and all three persistent *S. aureus* isolates had MICs of ≤0.5 μg/mL. This indicates that bacteriological response was not related to MICs in most cases. TABLE 11 shows the bacteriological response of organisms with MICs > 0.5 μg/mL in the European study.

As can be seen almost all of these pathogens were eradicated even the ones with an MIC of 4.0 μg/mL. Only at MICs of ≥ 8 μg/mL does a trend toward persisting isolates appear and then 2 of 5 isolates are still eradicated. This indicates that systemic breakpoints do not indicate bacteriological success rates for this topical otic product.

TABLE 11
Bacteriological Response for Organisms with MIC >0.5 μg/mL in European Study

Organism	MIC (μg/mL)			
	1.0	2.0	4.0	≥8.0
Enterococcus faecalis	9 (E)	1 (E)	–	1 (E) 1(P)
Pseudomonas aeruginosa	6 (E) 1 (P)	1 (E)	–	2 (P)
Peptostreptococcus	--	--	1 (E)	--
Streptococci Gp A,B,C,G	6 (E)	6 (E)	–	–
Bacteroides fragilis	--	--	–	1 (E)
Staphylococcus aureus	1 (E)	--	--	–
Streptococcus pneumoniae	1 (E)	–	–	–
Total	23 (E) 1(P)	8 (E)	1 (E)	2 (E) 3(P)

A summary of the clinical response of the predominant otitis externa organisms isolated during the European clinical trial is shown in TABLE 12. Clinical resolution or improvement occurred for 98% of *Pseudomonas aeruginosa*, 91% of *Staphylococcus aureus*, 95% of *Enterococcus faecalis*, and 95% of the *Enterobacteriaceae*. The overall failure rate was 4%.

TABLE 12
Clinical Response by Predominant Organisms in European Study

Organism (No.)	Resolution		Improvement		Failure	
	No.	%	No.	%	No.	%
Pseudomonas aeruginosa (245)	199	(81)	41	(17)	5	(2)
Staphylococcus aureus (47)	34	(72)	9	(19)	4	(9)
Enterococcus faecalis (23)	21	(91)	1	(4)	1	(4)
Enterobacteriaceae (19)	14	(74)	4	(21)	1	(5)
All organisms (386)	306	(79)	65	(17)	15	(4)

Comparison of USA and European Studies

Unlike the USA study, 22 strains of *Enterococcus faecalis* were isolated in the European Study. However, no *Stenotrophomonas maltophilia* or *Acinetobacter (anitratus) baumannii* were isolated in the European Study and these were two of the most prominent species isolated in the USA Study. TABLE 13 below shows the major organisms isolated in both clinical trials. The organisms from both the CIP-SOLN and the CIP-HC-SUSP groups are included since hydrocortisone does not effect bacteriological activity.

TABLE 13
Bacteriological Response by Organism (both trials)

	Eradicated/Presumed Eradicated		Persistence		Total (US + Eur.)	
	US n (%)	EUR n (%)	US n (%)	EUR n (%)	Erad/Pres Erad n (%)	Persist n (%)
P. aeruginosa	275 (99)	184 (90)	4 (01)	20 (10)	459 (95)	24 (05)
S. aureus	29 (97)	41 (93)	1 (03)	3 (07)	70 (95)	4 (05)
E. faecalis	0 (0)	21 (95)	0 (0)	1 (05)	21 (95)	1 (05)
P. mirabilis	10 (100)	8 (100)	0 (0)	0 (0)	18 (100)	0 (0)
A. anitratus	15 (100)	0 (0)	0 (0)	0 (0)	15 (100)	0 (0)
S. maltophilia	11 (92)	0 (0)	1 (08)	0 (0)	11 (92)	1 (08)

From the microbiological viewpoint the following organisms may be listed in the package insert in the listing of organisms for which both ciprofloxacin has been shown to have *in vitro* activity and ciprofloxacin hydrocortisone suspension has been shown to be effective in clinical trials:

Since this application is for a topical product and no correlation has been established between MICs or zone diameter breakpoints and clinical efficacy, no breakpoints or susceptibility test methods will be listed in the label.

Since this product is for topical otic use and no correlation has been established between *in vitro* MICs and clinical outcome, the listing of organisms which have a MIC_{90} value less than or equal to the drug's susceptible breakpoint (which only has meaning in systemic infections) is inappropriate and this list should be deleted. Since this product will be used empirically in most cases, the causative organism will not be known and a second list of organisms is not appropriate.

APPEARS THIS WAY
ON ORIGINAL

OCT 3 1997
Roche
520

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW ~~OF SUPPLEMENT~~
3 October 1997

A. 1. NDA 20-805
APPLICANT: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

2. PRODUCT NAME: CIPRO® HC Otic Suspensions

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile otic preparation for instillation into the ear.

4. METHODS OF STERILIZATION:
The product is not manufactured as a sterile product. It is, however, subject to microbial limits specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of otitis externa in adults and children.

B. 1. DATE OF INITIAL SUBMISSION: 7 February 1997

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:

DMF	DMF	DMF	DMF
DMF	DMF	DMF	DMF
DMF	NDA 19-847	NDA 19-537	

4. ASSIGNED FOR REVIEW: 12 August 1997

C. REMARKS: This product is not manufactured as a sterile product. It had been suggested to the applicant that this product should be sterile in a pre-NDA meeting, but, the applicant stated that it would not be possible to sterilize the suspension either terminally or by filtration. Therefore, product labeling should emphasize that the product is not to be used in cases of where the tympanic membrane may be perforated. However, because

of the probability that the product will be clinically used in cases of perforated tympanic membranes, we feel that the product should be manufactured as a sterile product.

D. CONCLUSIONS: The application is approvable pending receipt of a commitment for microbiology issues.

/S/

3 October 1997

Paul Stinavage, Ph.D.

10/3/97

cc: Original NDA 20-805
HFD-520/Div. Files/K. Roche/F.V. LeSane/D. Matecka
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 3 October 1997
R/D initialed by P. Cooney

cc: Original to NDA 20-805 through PM KRoche/HFD-520
HFD-357/EA File
HFD-357/Docket File
HFD-205/FOI copy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-805

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DIV

MAY 27 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

SUBMISSION DATE:	February 7, 1997
NDA:	[redacted]
Products:	Cipro® HC OTIC Suspension
Sponsor:	BAYER CORPORATION Pharmaceutical Division 400 Morgan Lane West Haven, CT 06516
TYPE OF SUBMISSION:	Original Application
Reviewer:	Jenny Zheng, Ph.D.
Date received for reviewing:	2-26-97

SYNOPSIS:

Ciprofloxacin-hydrocortisone topical otic suspension was developed for the treatment of otitis externa. The formulation contains 0.2% ciprofloxacin and 1% hydrocortisone. The applicants of NDA 20-805 is requesting waive of an in vivo bioavailability study. The issue was discussed in IND submitted on February 6, 1995. The C_{max} following administration of 3 drop of otic solution (0.3 mg) would have been only 0.0075 mg/L assuming 100% bioavailability as if it were an intravenous (IV) dose given the fact that the C_{max} was 4-5 mg/L following IV administration of 200 mg of ciprofloxacin. Similarly, the C_{max} would have been 0.0016 mg/L basing the fact that the fact that C_{max} was 4 mg/L following oral administration of 750 mg ciprofloxacin. Both concentrations are below the limit of quantitation (0.05 mg/L) of ciprofloxacin in the plasma. Moreover, the Sponsor has cited a study by Force et al (1993) in that the ciprofloxacin could not be detected in the blood of pediatric patients with chronic suppurative otitis media treated with topical (otic) ciprofloxacin for 14 days (Force et al. Topical ciprofloxacin for chronic suppurative otitis media: systemic absorption, efficacy, and adverse effects. Pharmacotherapy 1993; 13:680 (Abstract)).

The C_{max} of hydrocortisone was calculated to be 23 ng/mL following 3 drops of topical administration (1.5 mg) assuming that absorption from the preparation is similar to that following an oral-dose of 20 mg which yields a C_{max} of 305 ng/mL. However, the endogenous cortisol concentrations range from ng/mL. Therefore, the absorbed hydrocortisone cortisol could not be differentiated from the endogenous cortisol. On the other hand, it was found only 1.18% hydrocortisone was absorbed following multiple dosing with topical hydrocortisone (Melendres et al. In vivo percutaneous absorption of hydrocortisone: multiple application dosing in man. Pharm Res 1992; 9:1164-1167).

RECOMMENDATION:

The information provided by the applicant to support a request for waiver of in vivo bioavailability is acceptable. From a clinical pharmacology/biopharmaceutics standpoint, the application is acceptable.

/S/

Jenny Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT signed by Frank Pelsor, Pharm.D., Team Leader /S/

cc:
Div. File: NDA 20-805
HFD-520 (N. Moledina, MO)
HFD-520 (M. Albuerne, MO, TL)
HFD-520 (F. LeSane, CSO)

HFD-340 (Viswanathan)
HFD-880 (DEPIII File)
HFD-880 (F. Pelsor, TL)
HFD-880 (J. Zheng, Reviewer)
CDR (Attn., B. Murphy)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-805

ADMINISTRATIVE DOCUMENTS

Section 13: Patent Information

The following information is hereby provided pursuant to 21 CFR 314.53(c):

Patent Number: U.S. Patent No. 4,670,444
Expiration Date: 9 December 2003
Type of patent: drug, drug product, method of use
Name of patent owner: Bayer Aktiengesellschaft
Agent: applicant (Bayer Corporation) resides in the US

Patent Number: U.S. Patent No. 4,844,902
Expiration Date: 11 February 2008
Type of patent: drug product
Name of patent owner: Bayer Aktiengesellschaft
Agent: applicant (Bayer Corporation) resides in the US

The undersigned declares that Patent No. 4,670,444 and 4,844,902 each cover the composition, formulation, and/or method of use of the ciprofloxacin product that is the subject of this application for which approval is being sought.

Carl E. Calcagni, R. Ph.
Vice President, Regulatory Affairs
Pharmaceutical Division
Bayer Corporation

PATENT CERTIFICATION

All Investigations relied upon by Bayer in this NDA were conducted by or for Bayer.

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-805 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Cipro® HC Otic Ciprofloxacin hydrochloride and hydrocortisone otic suspension Action: AP AE NA

Applicant Bayer Corporation Therapeutic Class 35

Indication(s) previously approved none
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application acute otitis externa (For supplement answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

✓ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

_____ 2/9/98
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-805
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/ ~~SOlmstead~~ (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CERTIFICATION IMPOSED BY GENERIC DRUG ENFORCEMENT ACT

Pursuant to section 306(k) of the Federal Food, Drug and Cosmetic Act, the applicant, Bayer Corporation, formerly Miles, Inc., certifies that, to the best of its knowledge and belief, Bayer Corporation did not and will not use in any capacity in connection with this application, NDA 20-805, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

Signed: _____

Carl E. Calcagni, R.Ph.
Vice President, Regulatory Affairs

Date: December 19 1996

Consult #847 (HFD-590)

CIPRO-HC Otic Suspension ciprofloxacin hydrochloride/hydrocortisone

There were no look-alike/sound-alike conflicts noted or misleading aspects found in the proposed proprietary name. However, the Committee feels the proper established name for this product should be (ciprofloxacin hydrochloride and hydrocortisone otic suspension). The sponsor may continue to keep "Otic Suspension" as a part of the proprietary designation, however, this is redundant.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 9/9/97, Chair
CDER Labeling and Nomenclature Committee

Date: 1/28/98

To: Bayer Corporation Pharmaceutical Division
Att: Ms. Ann Marie Assumma

From: Dorota Matecka, Ph.D.

Through: Norman R. Schmuff, Ph.D. 1/28/98
Chemistry Team Leader
Division of Special Pathogens and Immunologic Drug Products, HFD-590

Re: CMC Comments/NDA 20-805

Please address the following CMC comments regarding the NDA 20-805 (Cipro HC Otic Suspension):

1. Was the stability of the drug product evaluated using the linear regression analysis/confidence internal method described in the 1987 Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics?

2. Are the lots # 3678, 3679, 3680 (mentioned in the 12/1/97 amendment) sub-lots e.g. part of the same lot? If not, explain why stability data appear to be quantitatively the same at all time points for the compound, Bay P9357, 21-HC Comp A RRT 1.33, at

3. Please, revise the expiration dating from the requested 24 months to 18 months. The requested 24 month expiration dating is not supported by the data. Of the two lots packaged in the proposed market container/closure with real-time 24 months data, neither was manufactured at the proposed production site (M941201 and RB24051-43 were manufactured in West Haven) and neither was manufactured at the proposed production scale. In addition, the second lot (RB24051-43) was not manufactured with the grade of proposed in the market formulation. Data on the other primary stability batches extend only to 44-46 weeks.

4. Please, lower the limits for the degradation products in the specifications for the drug product as follows:

Degradation products of ciprofloxacin:
compound: from "max. w/w" to "max. % w/w"
Bay P9357 from "max. %" area" to "max. % area"

Degradation products of hydrocortisone:
from "max. % area" to " max. % area"
HC Comp. A RRT 1.33 from "max. % area" to "max. % area"
from "max % area" to "max. % area"
Sum of HC Related Unknown from "max. % area" to "max. % area"
Sum of All HC Degradation Products from "max. % area" to "max. % area"

cc: Orig NDA
HFD-520

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-805

Bayer Corporation
Attn: Ann Marie Assumma
Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

JAN 20 1998

Dear Ms. Assumma,

Please refer to your new drug application (NDA) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cipro HC Otic Suspension.

We also refer to the teleconference between representatives of your firm and the Food and Drug Administration, Division of Anti-Infective Drug Products on September 4, 1997.

A copy of our minutes of that teleconference are enclosed.

Should you have any questions, please contact:

Kim Roche
Project Manager
Telephone: (301) 827-2125

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

RECORD OF TELECONFERENCE

DATE: September 4, 1997

SPONSOR: Bayer Corporation

NDA Number: 20-805
Drug: Cipro HC Otic Suspension

Meeting Chair: Eric Mann, M.D., Medical Officer

Meeting Recorder: Kim Roche, M.S., Project Manager

FDA attendees: Paul Flyer, Ph.D., Statistical Team Leader
Eric Mann, M.D., Medical Officer
Rosemary Roberts, M.D., Medical Team Leader
Kim Roche, M.S., Project Manager
Greg Soon, Ph.D., Statistical Reviewer

Bayer attendees: Anne Marie Assumma, M.S., Associate Director, Regulatory Affairs
Dan Haverstock, Associate Director, Statistics and Data Systems
Allen Heyd, Ph.D., Director, Anti-Infectives, Medical Research
Steven Jungerwirth, M.D., Director, Anti-Infective Medical Research
Minghua Shan, Ph.D., Senior Statistician
Andrew Verderame, Senior Regulatory Compliance Associate

Meeting Objective: To discuss the agenda items (see attachment).

Discussion Points:

1) End of Therapy Visit (EOT): The Sponsor chose a window of 3-7 days post-therapy, this was found to be acceptable during the IND review of the protocol. This is sufficient time off therapy to detect early clinic relapses. The Division provided histograms to the Sponsor on August 14, 1997, which demonstrated 739 patients evaluated for efficacy. There were 19 patients at day zero which fell outside the Sponsor's defined window. In addition, some patients were seen only one to two days after the drug was completed. The Medical Officer explained that day 3 should be considered the earliest time point and that day 10 would be acceptable as the EOT. Asked the Sponsor for clarification.

- The Sponsor's Cipro HC team agreed that day 3-10 would be a reasonable EOT time window. Agreed with the Division that the earlier visits should not be included in the analysis. Also want consistency for both U.S. and European studies.

- The Divisional review team asked the Sponsor to obtain internal concurrence for the 3-10 day window, generate data using the expanded window, and resubmit the data for review to the

Division. Asked the Sponsor to provide a time frame for notification of their decision to the Division. In addition, requested the Sponsor provide demographic information on patients excluded from the efficacy population including scores for acute otitis externa at baseline (edema, tenderness, otalgia) and clinical response.

- The Sponsor agreed to seek internal concurrence and provide the Division with a time frame.

2) Patients with residual otalgia were included in the improvement category in the Sponsor's NDA submission. However, the Medical Officer was concerned that these patients may have subsequently relapsed due to incompletely eradicated infection. Reference made to the letter of August 27, 1996 from the Sponsor (IND). Asked the Sponsor to provide the letter via facsimile and to submit the follow-up clinical efficacy determinations on patients with improvement at TOC visit.

3) Conflicting results with Time to End of Pain between studies:
The U.S. study demonstrated the contribution of components (addition of HC). The European study did not demonstrate a contribution.

The Sponsor maintained that the European results, although not attaining statistical significance, were supportive of the findings in the U.S. Time to End of Pain study.

4) In the U.S. study, time to end of pain was recorded in patient diaries. Asked for clarification of specific methods that were used in the European study to arrive at the end of pain.

- In the European studies, it was on an individual basis. The Sponsor will follow-up with European colleagues to determine details and convey findings to the Division. In the U.S. study a specific algorithm was used.

- The Medical Officer requests the Sponsor provide a random sample of case report forms (CRF) and diaries from Europe.

Agreed Upon/Action Items:
Sponsor:

1) To reach internal agreement on the expanded window of 3-10 days for the primary endpoint. Will convey decision to the Division and the time frame for decision.

2) To provide demographics on the patients less than 3 days versus those in the 3-10 day window.

3) To provide the August 27, 1996 letter via facsimile.

4) To provide data on the patients with improvement who had persistent otalgia at EOT; follow-up on these patients (cure versus relapse).

5) To provide analysis on the algorithm used in Europe.

Signature, minutes prepared by: 1/6/98 /S/

Concurrence Chair (or designated signatory): 1/6/98

cc:
Orig. NDA
HFD-520
HFD-725/StatsTL/Flyer
HFD-520/MO/Mann
HFD-520/PM/Roche
HFD-725/Stats/Soon

Concurrence only:
HFD-520/MTL/Roberts 1/9/98

Questions for Bayer: 14 August 1997

1. Why was the statistical plan altered to expand the time window for the End of Therapy Visit to include 1 through 10 days post-therapy? Was a protocol amendment submitted to the FDA regarding this change? Histograms for the End of Therapy Visit day for the valid for efficacy populations in both studies were generated from the SAS data sets and will be discussed during the scheduled meeting on August 18.

2. Why were patients with residual pain included in the "Improvement" category at the end of therapy time point? (e.g. Pt. No. in the European study)

3. How are the conflicting results for the Time to End of Pain analyses between the U.S. and European studies to be interpreted?

4. End of pain measurements:

    a. Why do some patients start with a "0" pain score when otalgia is a required evaluability criterion? (e.g. Pt. No. in European Study)
    b. Why are many of the "TIME/DATE PAIN ENDED" data entries blank on the tabulated patient diaries? (e.g. Pt. No. in European Study)
    c. How were patients who listed a positive pain score following a "0" pain score handled?
    d. Why are some of the severity scores blank for various time points? Can they be assumed to represent a pain score of "0"? (e.g. in European Study)
    e. Why were apparently different values/criteria used to determine time to end of pain? (e.g. Pt. No. in European Study)
    f. Clarification of how the U.S. and European studies differ in their determination of the time to end of pain endpoint (e.g. use of censoring)

5. Why was the study not investigator-blinded as recommended in the IND medical officer report?

6. How was a fungal isolate classified as a colonizer vs. a pathogen?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-805

Bayer Corporation
Attn: Ann Marie Assumma
Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

DEC 19 1997

Dear Ms. Assumma,

Please refer to your new drug application (NDA) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cipro HC Otic Suspension.

We also refer to the teleconference between representatives of your firm and the Food and Drug Administration, Division of Anti-Infective Drug Products on November 10, 1997.

A copy of our minutes of that teleconference are enclosed.

Should you have any questions, please contact:

Kim Roche
Project Manager
Telephone: (301) 827-2125

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

RECORD OF TELECONFERENCE

DATE: November 10, 1997

SPONSOR: Bayer

NDA Number: 20-805
Drug: Cipro HC Otic Suspension

Meeting Chair: Eric Mann, M.D., Medical Officer

Meeting Recorder: Kim Roche, M.S., Project Manager

FDA attendees: Eric Mann, M.D., Medical Officer
Rosemary Roberts, M.D., Medical Team Leader
Kim Roche, M.S., Project Manager

Bayer attendees: Steven Jungerwirth, M.D., Director, Anti-Infective Medical Affairs
Robert Kleinfield, Ph.D., Senior Project Manager
Minghua Shan, Ph.D., Senior Statistician
Andrew Verderame, Senior Regulatory Compliance Associate, RA

Meeting Objective: To discuss the agenda items (see attachment).

Discussion Points:

- Asked the Sponsor to explain the criteria used for superinfection versus colonization for fungal isolates in the European pathogen/organism database.

  The Sponsor will consult with European colleagues and provide follow-up with the Division next week.

- Asked the Sponsor for clarification on the revised "Time to End of Pain" data from the European study. Questioned whether patients with an initial pain score of 6 or greater could be followed until a pain score less than one was reported to determine if cipro HC had an improved effect versus cipro alone.

  The Sponsor explained that the study was not powered to look at a subset of the patients who had a moderate amount of pain. They were concerned about performing posthoc analysis of the data especially when the statistical power (i.e., number of patients) would be decreased.

  The Division agreed this was a valid point and it was agreed to request no further end of pain analysis.

- Request for the following updated tables including changes in the efficacy evaluable population (using the revised End of Treatment [EOT] time window) and correction of EOT efficacy determinations as per Sponsor's "Response to FDA Request for Information: Clinical" dated October 24, 1997: see listing of tables in attachment.

  Sponsor agreed to submit the tables as requested with end of treatment window (+3 to +10), corrected EOT determinations, and corrected bacterial efficacy database. The Sponsor asked if the data listings were necessary to support the summary tables. After internal discussion by the FDA review team, it was requested the Sponsor submit the data listings. In addition, it was agreed that the summary tables for the U.S. study should be submitted when available, and the European summary tables can be submitted at a later date.

  The Division expressed gratitude to the Sponsor for revising the tables to help expedite the review for completion by the PDUFA due date of February 10, 1998. Dr. Roberts outlined the internal time line for review and conveyed that the time line could be met with the Sponsor's continued assistance.

Agreed Upon/Action Items:

- The Sponsor will provide the Division with an explanation of the criteria used for superinfection versus colonization for fungal growth in the European pathogen/organism database after consulting with European colleagues next week.

- It was agreed no further end of pain analysis was necessary.

- Sponsor agreed to submit the tables as requested with end of treatment window (+3 to +10), corrected EOT determinations, and corrected bacterial efficacy database. It was requested the Sponsor submit the data listings. In addition, it was agreed that the summary tables for the U.S. study should be submitted when available, and the European summary tables can be submitted at a later date.

Signature, minutes prepared by: 12/11/97

/S/

Concurrence Chair (or designated signatory): 12/11/97

cc:
Orig. NDA
HFD-520
HFD-520/MO/Mann
HFD-520/PM/Roche

Concurrence only:
HFD-520/MTL/Roberts 12/12/97

11/10/97

Topics to be Discussed during Today's Teleconference Re: CIPRO HC Otic Suspension

1. The rationale for classification of fungal isolates as superinfection vs. colonization in the European study (e.g. Patient No.) at the End of Therapy Visit.

2. Discussion of revised "Time to End of Pain" data from the European study.

3. Request for the following updated tables including changes in the efficacy evaluable population (using the revised EOT time window) and correction of EOT efficacy determinations as per Bayer's "Response to FDA Request for Information: Clinical" dated October 24, 1997:

   Tables 1, 3, 4, 5, 17, 18, 19, 21, 23, 24, 29, 33 from both the U.S. and European studies

APPEARS THIS WAY
ON ORIGINAL

Cipro HC Otic Team Meeting

November 18, 1997

Attendees:
Eric Mann, Medical Officer
Rosemary Roberts, Medical Team Leader
Dorota Matecka, Chemistry Reviewer
Peter Dionne, Microbiology Reviewer
Amy Ellis, Pharmacology Reviewer
Greg Soon, Statistical Reviewer
Kim Roche, Project Manager

Statistical comments:

- European study- The Sponsor changed some patients from non-evaluable to evaluable. Greg will look at the data with Eric to address some questions.

  Bacterial data pending for European study; will follow-up with Sponsor next week.

- U.S. study- looks okay.

Microbiology comments:

- Review is complete.

- Need to determine if the Division will grant all organisms for indication.
  The Division needs to be consistent in labeling recommendations - Eric is working with Cheryl McDonald to look at the labeling for Ofloxacin.

- Regarding fungal isolates- The Sponsor classified some fungal isolates as pathogens. Reviewing European database.

- Unclear whether *Enterococcus faecalis* should be granted since all isolates were seen only in the European study.

Chemistry comments:

- Comments will be sent to both DMFs (for both drug substances: ciprofloxacine hydrochloride and hydrocortisone) via facsimile (after the meeting).

- Asked Sponsor to provide the updated stability data for the drug product: otic suspension.

- Inspection- initial inspection of manufacturing facility was unsatisfactory, one site needs follow-up inspection after problems are corrected. Dorota will ascertain the time frame required for re-inspection.

- Consult from Peter Cooney (August 1997)- determine if Sponsor has received these comments.

- Sponsor will need to put statement in labeling that this product can't be used in patients with perforated tympanic membranes since the product is not sterile (stated in pre-NDA meeting).

Medical comments:
- Several problems noted:
  initial window 3-7 days, Sponsor expanded the window to 3-10 days post-treatment.
  Follow-up visit
  Fungal isolate issue- described in Micro comments.

- Requested updated tables; received for U.S. study
  European data pending

- Working on first draft of review.

Pharmacology comments:
- 1 study pending- will be able to complete in several weeks

Agreed Upon/Action Items:
- Next team meeting to be held on December 16, 1997
- Schedule labeling meeting for mid-January 1998
- Eric & Greg will address concerns with European data base.
- Dorota will follow-up on time frame for re-inspection of manuf. site & will fax items re: DMF.
- Kim will convey Peter Cooney's comments to Sponsor.
- Amy will finish pending study in January.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-805

CORRESPONDENCE

NEW DRUG APPLICATION

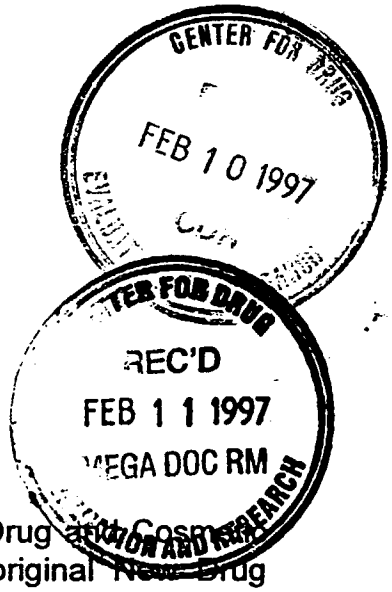
Bayer

Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

February 7, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
3rd Floor, Room N303
9201 Corporate Blvd.
Rockville, MD 20850



RE: NDA 20-805
CIPRO® HC OTIC SUSPENSION
ORIGINAL NEW DRUG APPLICATION

Dear Dr. Feigal:

In accordance with section 505 (b) (1) of the Federal Food, Drug and Cosmetic Act, Bayer Corporation, Pharmaceutical Division files this original New Drug Application for CIPRO HC Otic Suspension (ciprofloxacin hydrochloride, USP and hydrocortisone, USP).

CIPRO HC Otic Suspension contains ciprofloxacin hydrochloride, an anti-infective compound of the fluorinated carboxyquinolone group that has a broad range of activity against both Gram-negative and Gram-positive bacteria, combined with the anti-inflammatory corticosteroid, hydrocortisone, in suspension for otic use. Each mL of CIPRO HC Otic Suspension contains the active ingredients ciprofloxacin hydrochloride (equivalent to 2 mg ciprofloxacin), 10 mg hydrocortisone, and 9 mg benzyl alcohol as a preservative.

The efficacy and safety of the ciprofloxacin HC otic suspension formulation has been demonstrated in two large, controlled, multi-center, multi-national trials and form the clinical basis for this NDA. In addition, the ciprofloxacin HC otic suspension formulation clinical results show superiority in reducing the time to end of pain when compared to the ciprofloxacin otic solution containing no hydrocortisone, thus demonstrating the contribution of the hydrocortisone component in the ciprofloxacin suspension formulation.

Pharmacokinetic studies were not performed with this topical formulation. Included in this NDA, we have provided information to show that studies

designed to characterize the pharmacokinetic profile of the ciprofloxacin otic preparation or to characterize the pharmacokinetics of hydrocortisone following administration of the otic suspension formulation will not provide useful information. Ciprofloxacin serum concentrations will be below the detection limits and it will not be possible to distinguish the small contribution due to exogenous hydrocortisone from the endogenous cortisol concentration. Therefore, as discussed and previously agreed with the Division of Biopharmaceutics and members of your Division, we formally request a waiver for conducting pharmacokinetic studies for this formulation.

CIPRO HC Otic Suspension is intended for market by prescription for the treatment of acute diffuse bacterial external otitis caused by organisms susceptible to the action of ciprofloxacin, including *Pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter anitratus (baumannii), Proteus mirabilis, Stenotrophomonas maltophilia* and *Enterococcus faecalis.*

Included in this application are all clinical, statistical, pharmacokinetic and toxicology information as well as the chemistry, manufacturing and control data required for the review of this product. Also provided are Case Report Forms for all patients who died or discontinued therapy because of an adverse experience. Furthermore, the non-clinical pharmacology/pharmacokinetic and toxicology section, microbiology section, and clinical efficacy/safety section of this NDA also reference the ciprofloxacin tablet NDA 19-537 and the ciprofloxacin intravenous NDA 19-847.

This submission consists of an archival copy containing a total of 52 volumes, and review copies of each technical section. A third copy of Section 2.4 Summary of Chemistry, Manufacturing and Controls, Section 3 Chemistry, Manufacturing and Controls and Section 4 Methods Validation has been submitted to Mr. Richard Penta at the FDA District Office in Stoneham, MA.

As discussed during our pre-NDA meeting on November 18, 1996, Bayer does not intend to submit a CANDA in support of this NDA. However, data and reports would be made available in electronic form upon request from the reviewers.

Please refer to the attached Form 356h and accompanying NDA Index for details of the complete contents of this NDA. Please contact the undersigned at (203) 812-3290 if additional information or clarification is needed.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director, Regulatory Affairs

Encl.

Copy to : Ms. Frances LeSane, Project Manager (Cover Letter and Volume 1)

DESK COPY

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

February 9, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC OTIC
Response to FDA Request For Information : Package Insert

Dear Dr. Chikami,

Reference is made to the telephone conversation held earlier today between Mr. Andy Verderame of Bayer Corporation and Ms. Kim Roche of the Division of Anti-Infective Drug products. Ms. Roche asked for a few revisions to the package insert for the drug product, CIPRO HC OTIC.

These minor revisions have been made and faxed to the Division this afternoon. Please find a copy of Bayer's facsimile on the attached pages.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV

desk copy: Ms. Kim Roche, Project Manager

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

February 9, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC OTIC
Request for Pediatric Studies

Dear Dr. Chikami:

Reference is made to the facsimile message dated February 6, 1998 that was sent to your attention regarding the request for pediatric studies for CIPRO HC OTIC.

Enclosed for review and file is the cover letter that was submitted by facsimile.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Deputy Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

February 6, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
Third Floor, Room N303
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC OTIC
ORIGINAL NEW DRUG APPLICATION
Request for Pediatric Studies

Dear Dr. Chikami:

Our application for the new drug CIPRO HC Otic Suspension, NDA 20-805, is currently awaiting approval by the agency. The NDA would provide for the otic use of a combination of ciprofloxacin hydrochloride and hydrocortisone in adult and pediatric populations. This new drug would respond to an important medical need, particularly in pediatric patients.

Under the FDA Modernization Act of 1997 ("FDAMA"), FDA is authorized to request pediatric studies from NDA sponsors upon a determination that information on the use of a new drug in the pediatric population may produce health benefits in that population. An additional six months of market exclusivity is provided to NDA sponsors who submit such pediatric studies in response to a written request from the agency. See new Section 505A of the Federal Food, Drug and Cosmetic Act, as added by FDAMA. The legislative history of FDAMA indicates that data collected prior to the request may be used to satisfy a request for pediatric studies.

The information in the pediatric studies supporting NDA 20-805 will provide significant health benefits to the pediatric population. In recognition of the efforts of Bayer Corp. in developing this important new pediatric dosage form, we request that the agency issue a written request for the pediatric studies supporting the NDA under the procedures set forth in new Section 505A(a) of the Federal Food, Drug and Cosmetic Act, as added by FDAMA. A written request, including a time frame for completion and submission of the studies, is necessary in order to meet the criteria for additional exclusivity provided by FDAMA.

In response to such request, we would be able to immediately resubmit or refer to the pediatric studies supporting the NDA. Thus, these actions should not result in any delay in the approval of NDA 20-805.

Sincerely yours,

Carl E. Calcagni, R.Ph.
Vice President,
Regulatory Affairs

CEC:pc

Bayer

June 9, 1997

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
3rd Floor, Room N303
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
FOUR-MONTH SAFETY UPDATE

Dear Dr. Feigal:

In accordance with 21CFR 314.50(d)(5)(vi)(b), we hereby submit the Four-Month Safety Update to NDA 20-805 for CIPRO® HC Otic Suspension (ciprofloxacin hydrochloride, USP and hydrocortisone, USP), which was filed on February 7, 1997 and received by the Division on February 10, 1997.

At this time, we report that there is no new safety information available for this NDA. The clinical studies reported in the NDA were complete as reported and no further studies were conducted with this drug product. In addition, there have been no preclinical studies to report since the NDA was filed.

Please contact the undersigned at (203) 812-3290 if additional information or clarification is needed.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director, Regulatory Affairs

Copy to : Ms. Frances LeSane, Project Manager (Cover Letter)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
Bayer Corporation Pharmaceutical Division

DATE OF SUBMISSION
August 7, 1997

ADDRESS *(Number, Street, City, State and ZIP Code)*
400 Morgan Lane
West Haven, CT 06516

TELEPHONE NO. *(Include Area Code)*
(203) 812-3290

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
NDA 20-805

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Ciprofloxacin hydrochloride/Hydrocortisone

PROPRIETARY NAME *(If any)*
Cipro® HC OTIC Suspension

CODE NAME *(If any)*
BAY o 9867

CHEMICAL NAME Ciprofloxacin Hydrochloride: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid
Hydrocortisone: pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-, (11B)-

DOSAGE FORM
Liquid Suspension

ROUTE OF ADMINISTRATION
Otic

STRENGTHS(S)
0.2% Ciprofloxacin
1% Hydrocortisone

PROPOSED INDICATIONS FOR USE
Acute Diffuse Bacterial External Otitis

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

DMF DMF DMF DMF DMF
DMF DMF DMF DMF
NDA 19-847
NDA 19-537

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG

HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* Response to Request for Information

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Summary (21 CFR 314.50) (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
X	15. OTHER *(Specify)* Response to Request for Information

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Ann Marie Assumma, M.S. Assoicate Director, Regulatory Affairs	Ann Marie Assumma	August 7, 1997

ADDRESS *(Street, City, State, ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
400 Morgan Lane West Haven, CT 06516	(203) 812-3290

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Nancy Sager, Enviromental Team Leader
(Desk Copy)

Bayer

November 21, 1997

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: ENVIRONMENTAL ASSESSMENT

Dear Dr. Chikami:

Reference is made to the telephone conversation with Kim Roche, Project Manager and a subsequent telephone conversation with Nancy Sager, Environmental Team Leader on October 1 regarding the request for a revised environmental assessment report for CIPRO® HC Otic Suspension, NDA 20-805.

Enclosed for review and files are two (2) copies of the environmental assessment report (format items 1 - 15). Please note that extensive reference has been made in this document to the environmental assessment report for CIPRO Oral Suspension, NDA 20-780, as discussed with Nancy Sager. For ease of review and expediency, desk copies of this document are provided to the project manager and chemistry reviewers. As noted, this is a public document.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Desk Copy)
Nancy Sager, Environmental Team Leader (Desk Copy)
Dorota Matecka, Review Chemist (Desk Copy)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

August 7, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
GENERAL CORRESPONDENCE: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Chikami:

Reference is made to the teleconference call dated July 31, 1997 with Ms. Kim Roche, Project Manager and Dr. Greg Soon, Statistical Reviewer from your Division and Dr. Michael Shan, Statistician and Mr. Dan Haverstock, Statistician and myself from Bayer to discuss the additional information that Dr. Soon needs to continue his review of the subject NDA.

Further to this discussion, we received a facsimile message dated August 1 from Ms. Roche which detailed three additional points concerning statistical information that Dr. Soon had requested.

Enclosed for review and files is one volume which contains the following information which address Dr. Soon's comments from the August 1 facsimile message and from the teleconference call from July 31:

- Written responses to the three items from Dr. Soon listed on the August 1 facsimile message;

- Algorithms used to calculate the efficacy variables from the source data, entitled, "Summary of rules used in the calculation of organism bacteriologic response", "Summary of rules used in the calculation of site (ear) bacteriologic response", and "Summary of rules used in the calculation of site-level (ear) time to end of pain;

- Main Patient-level Efficacy Variables in Dataset DEMO for clinical studies D94-008 and SN 1439;

- Annotated Case Report Form for D94-008.

  Please note that the annotated case report form for SN 1439 is the same as for D94-008, therefore only one copy was included here.

- Diskette containing the study SN 1439 datasets and format library and the SAS code for calculating the main efficacy variables in SAS 6.1x format. Also included is a copy of the printout of the SAS code.

I trust that the enclosed information is sufficient for Dr. Soon's needs. However, if further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

/AMA

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Greg Soon, Statistical Reviewer, Room N438 (Desk Copy)

COVER LETTER:
MS. KIM ROCHE

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

August 14, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated August 1, 1997 from Ms. Kim Roche, Project Manager which contained several comments from the medical reviewer, Dr. Eric Mann concerning the subject NDA.

On August 7, 1997, we provided one volume which addressed a number of Dr. Mann's comments from the August 1 facsimile message. As discussed with Ms. Roche during our telephone call of August 6 we indicated that, for Comment (1), case report forms and original patient score diaries from 5% of the intent-to-treat patient population using the randomized list generated by the statistician (attached to the August 1 facsimile message) would be provided under separate cover.

Enclosed for review and files are two (2) copies of five (5) volumes each of the case report forms requested for the US clinical study report, D94-008. A listing of the case report forms as they ordered in the August 1 request precedes the submission.

Please note that the case report forms for the European study report, SN 1439, have been requested of our European colleagues, and these will be forwarded as soon as they are available.

I trust that the enclosed information is sufficient for Dr. Mann's needs at this time. However, if further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

/AMA

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Cover Letter)

Ms. Kim Roche
Project Manager

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

September 8, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated August 1, 1997 from Ms. Kim Roche, Project Manager which contained several comments from the medical reviewer, Dr. Eric Mann concerning the subject NDA.

On August 14, 1997, we provided five volumes of the case report forms requested for the US clinical study report, D94-008. We indicated that the requested case report forms for the European study report, SN 1439, would be provided under separate cover.

Enclosed for review and files are two (2) copies of four (4) volumes each of the case report forms for the European study report, SN 1439. A listing of the case report forms as they were ordered in the august 1 request precedes the submission.

For your information, we have received follow-up information regarding patient in the European study and we are in the process of translating the document. This is the last outstanding item from the August 1 facsimile message.

I trust that the enclosed information is sufficient for Dr. Mann's needs at this time. However, if further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

/AMA

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Cover Letter)

BH
ORIG AMENDMENT

Bayer

ORIGINAL

Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

September 18, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the teleconference call on September 4, 1997 with Bayer representatives and members of your Division concerning several comments on the pivotal clinical study reports for the subject NDA.

Specifically, in summary of this teleconference discussion, Bayer agreed to: Provide the re-analysis of the clinical efficacy data for those valid patients who had a clinical evaluation performed 3 - 10 days following their end of therapy for the clinical studies D94-008 (US) and SN 1439 (Europe); to provide the demographics for the patients in the 3 - 10 day efficacy analysis and the demographics for the patients treated 0 - 2 days who were excluded from the new 3 - 10 day efficacy analysis for these studies; to provide the lists of patients (using the 3 - 10 day window) who had a clinical outcome of improvement at the end of therapy with residual otalgia, and their clinical outcome at the two-week follow-up and; to provide clarification of the time to end of pain measurement for the European clinical study SN 1439.

Enclosed for your review and files are two (2) copies of one (1) volume containing the requested information as described above. Please note that a desk copy containing this information is provided directly to Dr. Eric Mann, medical reviewer for convenience of review.

D94-008

SN 1439

pain - SN 1439

I trust that the enclosed information is sufficient for continuation of the clinical review of this NDA at this time. However, if further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

/AMA

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy)

Ms. Kim Roche/Project Manager

Cover Letter

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

September 30, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated August 1, 1997 from Ms. Kim Roche, Project Manager which contained several comments from the medical reviewer, Dr. Eric Mann concerning the subject NDA.

We have previously provided the response to Comment (1), case report forms and original patient score diaries from 5% of the intent-to-treat patient population using the randomized list generated by the statistician (attached to the August 1 facsimile message). However, the laboratory culture reports for these patients were not included as part of the case records. This was noted by Ms. Roche in a recent conversation with her.

Enclosed for review and files is one (1) volume which contains the lab culture reports to accompany the case report forms for those patients that were previously submitted for the US clinical study report, D94-008. A listing of the lab culture reports for the patients as they were ordered in the August 1 request precedes the submission. Please note that there was no culture taken for patient Therefore, no culture report is available for this patient.

Please note that the lab culture reports for the European study report, SN 1439, have been requested of our European colleagues, and these will be forwarded as soon as they are available.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

/AMA

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy)

Bayer

October 3, 1997

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated August 1, 1997 from Ms. Kim Roche, Project Manager which contained several comments from the medical reviewer, Dr. Eric Mann concerning the subject NDA. Specifically, there was one remaining issue regarding the response to Comment (7) where Dr. Mann requested the case report form and any available studies (audiograms, evoked potentials, etc.) related to the workup of the sudden hearing loss in patient in the European study. This should include any further workup of the hearing loss since the NDA submission.

Enclosed for your review and files are two (2) copies of one (1) volume containing the requested information as described above. Please note that the follow-up information on this patient was sent by facsimile message to your Division on September 24.' We are providing a desk copy containing the enclosed information directly to Dr. Eric Mann, medical reviewer for convenience of review.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy)

Ms. Kim Roche, Project Manager

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

October 10, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated September 23, 1997 from Ms. Kim Roche, Project Manager which contained several comments from the medical reviewer, Dr. Eric Mann concerning the subject NDA.

Enclosed for review and files are responses to Comments 1(a) through 1(d) of the facsimile message concerning the questionable "End of Therapy" clinical efficacy determinations for the four patients listed in the US and European clinical trials.

For your information, we have indicated in our partial response to Comment 2 regarding no "End of Therapy" evaluation for the listed patients in the European clinical trial that these are being prepared in the re-analysis and will follow under separate cover.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy)

Ms. Kim Roche
Project Manager

Bayer

October 15, 1997

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to our correspondence to you dated September 30, 1997 in which we provided the laboratory culture reports to accompany the case report forms for those patients that were previously submitted for the US clinical study D94-008 as part of the review for NDA 20-805. Previously, we also provided the case report forms and patient diaries for the requested patients in the European study SN 1439, and we noted that the culture data for these patients would follow under separate cover.

Enclosed for review and files is one (1) volume which contains the lab culture reports to accompany the European clinical study report, SN 1439. A listing of the lab culture reports for the patients as they were ordered in the August 1 request precedes the submission.

We trust that this information completes all of the requested information from the August 1 facsimile message from Ms. Kim Roche. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy)

Ms. Kim Roche, Project Manager

Bayer

Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

October 17, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated October 3, 1997 from Ms. Kim Roche, Project Manager which contained a request from the medical reviewer, Dr. Eric Mann for revision of "Time to End of Pain" analysis for the European study SN 1439 using the US study guidelines and statistical methods from study D94-008 for the subject NDA. Specifically, it was noted by Dr. Mann that the use of censoring and harmonization of the pain scale measurements with the "Time/Date Pain Ended" field differed between the two studies, and therefore the re-analysis will facilitate meaningful comparisons of the two studies.

Enclosed for review and files are the following:

- Explanation of the Analysis of the Original SN1439 Time to End of Pain data using the US method, including a graphic representation of the observations for the patients valid for efficacy for the three treatment groups;

- Study SN 1439 Patient Data Tabulations for "Date/Time Pain Ended" reported in Patient Diaries according to the re-analysis using the US method;

- Diskette containing the SAS datasets for the re-analysis of the original time to end of pain data using the US method, including the program for survival analysis and to create the graph. A list of the files included on the diskette is also enclosed. (Please note that the desk copy of the diskette is included for Dr. Zoon only.)

gave to Greg
10/20

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy, minus diskette)
Dr. Greg Soon, Statistician, HFD-725, Room N438 (Desk Copy, including diskette)

Ms. Kim Roche

Bayer

Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

October 24, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated September 23, 1997 from Ms. Kim Roche, Project Manager which contained several comments from the medical reviewer, Dr. Eric Mann concerning the subject NDA.

Further reference is made to our responses dated October 10 to Comments 1(a) through 1(d) of the facsimile message concerning the questionable "End of Therapy" clinical efficacy determinations for the four patients listed in the US and European clinical trials. We also included a partial response to Comment 2 of the facsimile message, indicating that a full response would follow under separate cover.

Enclosed for your review and files are the following information regarding no "End of Therapy" evaluation for the listed patients in the European clinical trial:

- Appendix I contains the written response to Comment (2) regarding no "End of Therapy" evaluation;
- Appendix 2 contains the algorithm for determining the ear level EOT clinical response for the new re-analysis of the SN 1439 clinical response data;
- Appendix 3 contains the re-analysis of the SN 1439 clinical response data;
- Appendix 4 contains a listing of the 30 patients who are included in the re-analysis of the SN 1439 clinical response data.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.

Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy)

Ms. Kim Roche, Project Manager

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

October 31, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
3rd Floor, Room N303
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO HC Otic Suspension
Response to FDA Request For Information : Clinical

Dear Dr. Chikami,

Reference is made to the facsimile message dated October 9, 1997 from Kim Roche, Project Manager, which contained a request from the Medical Reviewer, Dr. Eric Mann, for information on the referenced causative organisms of acute, diffuse otitis externa.

Bayer 's response follows on the attached pages. Also included are several literature references to support Bayer's position that the referenced organisms are causative pathogens and the data presented in the NDA is sufficient to substantiate their inclusion in the INDICATIONS AND USAGE section of the package insert.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director, Regulatory Affairs

/ASV
enclosures

desk copy: Dr. Eric Mann, Medical Reviewer, Room F310
Ms. Kim Roche, Project Manager (cover letter)

Ms. Kim Roche, Project Manager
Personal & Confidential

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

November 7, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the telephone conversations dated November 4 and 5, 1997 with Ms. Kim Roche, Project Manager concerning additional information for NDA 20-805 requested by the medical reviewer, Dr. Eric Mann and the statistical reviewer, Dr. Greg Soon.

Specifically, there are three issues that need to be addressed: (1) The "Time to End of Pain" analysis for both the US and European studies using the 3 - 10 day End of Therapy window; (2) Copy of the diskette containing re-analysis of the US and European clinical response data using the 3 - 10 day End of Therapy window and; (3) Copy of the diskette containing the re-analysis of the US and European bacteriological response data using the 3 -10 day End of Therapy window.

Enclosed for your review and files are the following information regarding the information requested:

- Appendix I contains the listing of patients from the US study, D94-008 for the "valid for clinical efficacy analysis" using the 3 - 10 day End of Therapy window;

- Appendix 2 contains the graph for the analysis of "Time to End of Pain" data for the US study, D94-008 using the 3 - 10 day End of Therapy window;

- Appendix 3 contains the re-analysis of the bacteriological response for the US study D94-008 for the patients valid for efficacy analysis using the 3 - 10 day End of Therapy window;

- Appendix 4 contains the listing of patients from the European study, SN 1439-for the "valid for clinical efficacy analysis" using the 3 - 10 day End of Therapy window;

- Appendix 5 contains the graph for the analysis of "Time to End of Pain" data for the European study using the 3 - 10 day End of Therapy window;

- Diskette (desk copy for Dr. Soon only) containing the datasets of the new efficacy data using the 3 - 10 day End of Therapy window for the US study D94-008 for clinical response, bacteriological response and "Time to End of Pain" and for the European study SN 1439 for clinical response, and "Time to End of Pain.

  Please note that the bacteriological response for the European study SN 1439 will follow under separate cover;

- Desk copy for Dr. Soon of our October 24, 1997 correspondence which contains the algorithm for determining the ear level End of Therapy clinical response for the new re-analysis of the European study SN 1439 clinical response data, as well as the re-analysis of the SN 1439 clinical response data.

Please note that the re-analysis of the "Time to End of Pain" using the 3 - 10 day End of Therapy window for both the US and European studies was not done with our October 17, 1997 correspondence (which included the response to Dr. Eric Mann's October 3 facsimile message) since the patient information for the time to end of pain is unaffected by the change in the end of therapy window.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy)
Dr. Greg Soon, Statistical Reviewer, HFD-725, Room N438 (Desk Copy, including diskette)

Ms. Kim Roche, Project Manager
(Cover Letter)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

November 14, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated November 10, 1997 from your Division and the telephone conversation dated November 10, 1997 with Ms. Kim Roche, project manager, Dr. Eric Mann, medical reviewer and Dr. Rosemary Roberts, medical team leader, and representatives from Bayer concerning additional information for NDA 20-805 requested by Dr. Mann.

Specifically, there are three issues that need to be addressed: (1) The classification of fungal isolates as superinfection vs. Colonization in the European study at the End of Therapy Visit; (2) Discussion of revised "Time to End of Pain" data from the European study; and; (3) Request for the following updated tables including changes in the efficacy evaluable population (using the revised EOT time window) and correction of EOT efficacy determinations as per Bayer's "Response to FDA Request for Information: Clinical" dated October 24, 1997 (Tables 1, 3; 4, 5, 17, 18, 19, 21, 23, 24, 29, 33 from both the US and European studies).

Enclosed for your review and files are the following information regarding the information requested:

- Appendix I contains the response to comment (2) concerning the exploratory analyses discussed during the November 10 teleconference and the graphs and summary tables that were also sent via facsimile message today;

- Appendix 2 contains the revised tables in response to comment (3) for the US study only. Please note that we have also included table 19A, which includes confidence intervals for differences in rates of success, not controlling for possible center effect, which may be useful for review purposes.

- Diskette (in Word format) containing the revised tables included in the response to comment (3) for the US study only. A desk copy of this diskette is provided directly to Dr. Mann.

Please note that the response to comment (1) for the European study and the revised tables to respond to comment (3) for the European study will follow under separate cover within the next several days.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy, including diskette)

Bayer

November 21, 1997

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: ENVIRONMENTAL ASSESSMENT

Dear Dr. Chikami:

Reference is made to the telephone conversation with Kim Roche, Project Manager and a subsequent telephone conversation with Nancy Sager, Environmental Team Leader on October 1 regarding the request for a revised environmental assessment report for CIPRO® HC Otic Suspension, NDA 20-805.

Enclosed for review and files are two (2) copies of the environmental assessment report (format items 1 - 15). Please note that extensive reference has been made in this document to the environmental assessment report for CIPRO Oral Suspension, NDA 20-780, as discussed with Nancy Sager. For ease of review and expediency, desk copies of this document are provided to the project manager and chemistry reviewers. As noted, this is a public document.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Desk Copy)
Nancy Sager, Environmental Team Leader (Desk Copy)
Dorota Matecka, Review Chemist (Desk Copy)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

December 1, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC OTIC SUSPENSION
Response to FDA Request For Information : Chemistry

Dear Dr. Chikami,

Reference is made to the facsimile message dated November 18, 1997 from Kim Roche, Project Manager, which contained a request from the CMC Reviewer, Dr. Dorota Matecka, for updated information concerning the stability of the drug product.

Bayer's response follows on the attached pages. Note that this response includes copies of updated documentation which reference the previously unidentified ciprofloxacin related compound, RRT 2.7. This compound has been identified as Bay p 9357, ciproformamide. During a discussion with Dr. Matecka held on November 25, 1997, it was agreed that Bayer would provide the current documentation to maintain the completeness of the Division's file on this drug product.

Also note that Bayer's response to the questions posed about the drug substance DMF will follow under separate cover.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director, Regulatory Affairs

/ASV
appendices

desk copy: Dr. Dorota Matecka, Chemistry Reviewer
Ms. Kim Roche, Project Manager (cover letter)

ORIGINAL

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

December 2, 1997

Gary Chikami, M.D., Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the facsimile message dated November 10, 1997 from your Division and the telephone conversation dated November 10, 1997 with Ms. Kim Roche, project manager, Dr. Eric Mann, medical reviewer and Dr. Rosemary Roberts, medical team leader, and representatives from Bayer concerning additional information on the US and European pivotal clinical studies for NDA 20-805 requested by Dr. Mann.

Subsequently on November 14, we provided our responses and revised tables for the US clinical study only and we indicated that the responses and revised tables for the European study would follow under separate cover.

Specifically, there are three issues that need to be addressed regarding the European clinical study, SN 1439: (1) The classification of fungal isolates as superinfection vs. Colonization in the European study at the End of Therapy Visit; (2) Discussion of revised "Time to End of Pain" data from the European study; and; (3) Request for the following updated tables including changes in the efficacy evaluable population (using the revised EOT time window) and correction of EOT efficacy determinations as per Bayer's "Response to FDA Request for Information: Clinical" dated October 24, 1997 (Tables 1, 3, 4, 5, 17, 18, 19, 21, 23, 24, 29, 33 from the European study).

Enclosed for your review and files are the following information regarding the information requested for the European clinical study:

- Appendix I contains the response to comment (1) concerning the rationale for the classification of fungal isolates as superinfection vs. colonization in the European study;

- Appendix 2 contains the revised tables in response to comment (3) for the European study. Please note that we have also included table 19A, which includes confidence intervals for differences in rates of success, not controlling for possible center effect, which may be useful for review purposes. Please note that Table 33 contains the analysis of the Time to End of Pain using the US method;

- Diskette (in Word format) containing the revised tables included in the response to comment (3) for the European study. Please note that, for Table 33, the graph could not be translated into Word format, therefore only the table appears. A desk copy of this diskette is provided directly to Dr. Mann.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Associate Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Eric Mann, Medical Reviewer, Room F310 (Desk Copy, including diskette)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203-812-2000

December 22, 1997

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC OTIC SUSPENSION
Response to FDA Request For Information : Chemistry

Dear Dr. Chikami,

Reference is made to the facsimile message dated December 12, 1997 from Kim Roche, Project Manager, which contained a request from the CMC Reviewer, Dr. Dorota Matecka, for additional information concerning the drug product, Cipro HC Otic Suspension.

Enclosed herein is Bayer's response to the first question of the Division's facsimile. This question asked Bayer to supply new Methods Validation Packages. These new packages include revised documentation which identifies the Cipro-related degradant in the drug product. Two copies are provided for the Division's review. An additional copy is being sent directly to Dr. Matecka for her convenience.

Also note that Bayer's response to the request for additional drug product documentation (Questions 2 through 6) will be submitted under separate cover.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Andrew S. Verderame

For: Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV
appendices

desk copy: Dr. Dorota Matecka, Chemistry Reviewer

ORIGINAL

Bayer

ONE ASSIGNMENT
BC

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

December 23, 1997

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC OTIC SUSPENSION
Response to FDA Request For Information : Chemistry

Dear Dr. Chikami,

Reference is made to the facsimile message dated December 12, 1997 from Kim Roche, Project Manager, which contained a request from the CMC Reviewer, Dr. Dorota Matecka, for additional information concerning the drug product, Cipro HC Otic Suspension.

Enclosed herein is Bayer's response to questions two through six of the Division's facsimile. Two copies are provided for the Division's review. An additional copy is being sent directly to Dr. Matecka for her convenience. This completes Bayer's response to the Division's December 12th questions.

Also note that Bayer's response to the request for additional drug product methods validation documentation (Question 1) has been submitted under separate cover.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV
appendices

desk copy: Dr. Dorota Matecka, Chemistry Reviewer

ORIGINAL

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

BJ

December 31, 1997

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC OTIC SUSPENSION
Response to FDA Request For Information : Microbiology

Dear Dr. Chikami,

Reference is made to the facsimile message dated November 18, 1997 from Kim Roche, Project Manager, which contained a request from the Microbiology Consultant, Dr. Peter Cooney, for an additional commitment concerning the microbiological testing of the drug product, Cipro HC Otic Suspension.

Enclosed herein is Bayer's complete response to the petition for additional microbiological testing. In summary, Bayer does commit to the requested preservative effectiveness and chemical assay testing.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Arduel Verdesmc

For: Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV

ORIGINAL

3L

Bayer

G Klamm
1/14/98
NAI

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

January 5, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC Otic Suspension
Response to FDA Request For Information

Dear Dr. Chikami,

Reference is made to the telephone discussion held January 2, 1998 between Ms. Kim Roche, Anti-Infective Project Manager, and Mr. Andrew S. Verderame of Bayer. Ms. Roche indicated that an electronic diskette copy of the Bayer proposed draft labeling from the original NDA would aid the Division in its review of the Cipro HC Otic Suspension submission.

Bayer is pleased to provide two copies of the diskette containing:

- file Oticpi.doc, which contains the Bayer proposed package insert for Cipro HC Otic Suspension as presented in the original NDA.

This file is presented in WORD 7.0 format. Note that one copy of the diskette is being sent directly to Ms. Roche for her convenience.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma

Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV
enclosure

desk copy: Ms. Kim Roche, Project Manager (cover letter and diskette)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

January 7, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the teleconference call dated November 10, 1997 with members of your Division and representatives from Bayer concerning additional information on the US and European pivotal clinical studies for NDA 20-805. Further reference is made to the copy of the record of this teleconference call which we received from you dated December 19, 1997.

Specifically, we agreed to provide the patient data listings for the US and European pivotal studies which support the summary tables previously provided for these studies where: The end of treatment window was revised to +3 to +10 days; the corrections were made to the End of Therapy determinations; and the corrections were made to the bacterial efficacy database.

Enclosed for your review and files are fifteen (15) volumes containing the revised patient data listings for the European study SN 1439.

Please note that we are providing under separate cover the revised patient data listings for the US study D94-008.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Deputy Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

January 9, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC Otic Suspension
Response to FDA Request For Information

Dear Dr. Chikami,

Reference is made to the telephone discussion held January 8, 1998 between Ms. Kim Roche, Anti-Infective Project Manager, and Mr. Andrew S. Verderame of Bayer. Ms. Roche indicated that an electronic diskette copy of the Bayer proposed draft labeling from the original NDA would aid the Division in its review of the Cipro HC Otic Suspension submission. She further advised that it was difficult to access the previous diskette (Word 7.0) sent on January 5th as it was not compatible with the personal computer in her office.

Therefore, Bayer is pleased to provide two new copies of a diskette containing:

- file OTICPI1.wpd, which contains the Bayer proposed package insert for Cipro HC Otic Suspension as presented in the original NDA.

This file is presented in WordPerfect 6.1 format as requested by Ms. Roche. Note that one copy of the diskette is being sent directly to Ms. Roche for her convenience.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV
enclosure

desk copy: Ms. Kim Roche, Project Manager (cover letter and diskette)

Bayer

January 15, 1998

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CHEMISTRY

Dear Dr. Chikami:

Reference is made to the facsimile message dated January 12, 1998 from Ms. Kim Roche, Project Manager, which contained requests from the chemistry reviewer, Dr. Dorota Matecka, for additional information concerning the drug substance, ciprofloxacin hydrochloride, and the otic suspension drug product.

Enclosed herein are Bayer's responses to the three (3) comments on the otic suspension drug product (see Attachment 1). Two (2) copies are provided for the Division's review. An additional copy is being sent directly to Dr. Matecka for convenience of review.

Please note that we are providing under separate cover within the next several days the responses to the ciprofloxacin hydrochloride drug substance comments. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Deputy Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)
Dr. Dorota Matecka (Desk Copy)
NDA File Copies (2)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 937-2000

January 21, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-805
CIPRO® HC Otic Suspension
RESPONSE TO FDA REQUEST FOR INFORMATION: CLINICAL

Dear Dr. Chikami:

Reference is made to the teleconference call dated November 10, 1997 with members of your Division and representatives from Bayer concerning additional information on the US and European pivotal clinical studies for NDA 20-805. Further reference is made to the copy of the record of this teleconference call which we received from you dated December 19, 1997.

Specifically, we agreed to provide the patient data listings for the US and European pivotal studies which support the summary tables previously provided for these studies where: The end of treatment window was revised to +3 to +10 days; the corrections were made to the End of Therapy determinations; and the corrections were made to the bacterial efficacy database.

Enclosed for your review and files are fifteen (15) volumes containing the revised patient data listings for the US study D94-008.

Please note that we provided under separate cover on January 7, 1998 the revised patient data listings for the European study SN 1439.

If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

Ann Marie Assumma, M.S.
Deputy Director
Regulatory Affairs

Encl.
Copy to: Ms. Kim Roche, Project Manager (Cover Letter)

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

January 23, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC OTIC SUSPENSION
Response to FDA Request For Information : Chemistry

Dear Dr. Chikami,

Reference is made to the facsimile message dated January 12, 1998 from Kim Roche, Project Manager, which contained a request from the Chemistry Reviewer, Dr. Dorota Matecka, for additional information concerning Drug Master File and the drug substance ciprofloxacin hydrochloride.

Bayer's response follows on the attached pages. Supporting documentation is provided in the appendices. We trust that this information is complete and will satisfy Dr. Matecka's requirements. In addition, Bayer commits that this updated documentation will be included in the next annual revision to DMF

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

For: Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV

desk copy: Ms. Kim Roche, Project Manager
Dorota Matecka, Ph.D., Chemistry Reviewer

Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

February 3, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-805
CIPRO® HC OTIC
Response to FDA Request For Information : Chemistry

Dear Dr. Chikami,

Reference is made to the facsimile message dated January 28, 1998 from Kim Roche, Project Manager, which contained four comments from the Chemistry Reviewer, Dr. Dorota Matecka, concerning the drug product CIPRO ® HC OTIC.

Bayer's response follows on the attached pages. Supporting documentation is also provided in the attached appendix. Please also refer to the Dec. 23, 1997 amendment for completeness. To briefly summarize Bayer's position, we believe that the data justify a 24 month expiration date but will for the time being accept 18 month dating. Stability documentation has been recreated for the Division which includes the regression analysis specified. Finally, Bayer agrees to change some specifications as described in the Division's January 28th facsimile. For some others Bayer proposes to compromise with the Division at a point in between Bayer's original specification and the Division's proposal, and for others still, Bayer believes it is justified to retain the original specifications. We trust that the information included in this response is complete and will satisfy Dr. Matecka's requirements.

Thank you for your attention to this application. If further information or clarification is needed, please contact me at (203) 812-3290.

Sincerely,

For: Ann Marie Assumma, M.S.
Deputy Director, Regulatory Affairs

/ASV

desk copy: Ms. Kim Roche, Project Manager
Dorota Matecka, Ph.D., Chemistry Reviewer