CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-277

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA#: 21-277

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	02-NOV-00
CDER DATE:	02-NOV-00
REVIEW ASSIGN DATE:	18-NOV-00
REVIEW COMPLETE DATE:	02-MAR-01

SPONSOR: Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON: Andrew S. Verderame
Associate Director Regulatory Affairs
Phone Number: (203) 812-5172

SUBMISSION REVIEWED: Original NDA Submission

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

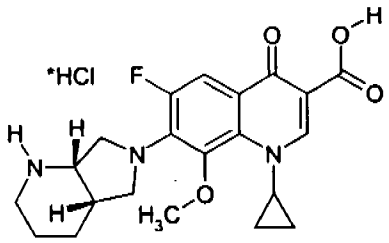
INDICATIONS: Community-acquired pneumonia (CAP), acute sinusitis, and acute bacterial exacerbations of chronic bronchitis (ABECB)

DOSAGE FORM: 400 mg intravenous solution

DRUG PRODUCT NAME

PROPRIETARY: Avelox™
NONPROPRIETARY/USAN: Moxifloxacin Hydrochloride
CODE: BAY 12-8039
CHEMICAL NAME: (1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo(4.3.0)non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolone carboxylic acid hydrochloride

STRUCTURAL FORMULA:



Molecular Formula: $C_{21}H_{24}FN_3O_4 \bullet HCl$
Molecular Weight: 437.9

SUPPORTING DOCUMENTS:

[redacted]

NDA #21-085—Moxifloxacin Tablets (approved 12/10/99)

REMARKS/COMMENTS:

This original New Drug Application is for AVELOX (moxifloxacin hydrochloride) I.V. Solution. The active ingredient in AVELOX I.V. is moxifloxacin hydrochloride, which is the same drug substance as used in AVELOX Tablets, NDA 21-085. The tablet application was approved in December 1999. Included in this application are data to show that oral and intravenous 400 mg dosing are bioequivalent. Bayer has also included information on two community-acquired pneumonia clinical trails. Bayer is requesting approval of penicillin-resistant *Streptococcus pneumoniae* in this application for the treatment of community-acquired pneumonia and acute sinusitis.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY subsection of the package insert. Combining the I.V. and Tablet community-acquired pneumonia studies (CAP) there were 13 penicillin-resistant (MIC ≥2 µg/mL) *Streptococcus pneumoniae* isolates. Seven of these isolates, however, had penicillin susceptibility determined only by the E-test method. These isolates were all from centers outside of the United States and the penicillin MIC could not be determined by broth dilution. Six of the seven had penicillin-MICs of 1.5 or 2.0 µg/mL. Since the E-test method may give a MIC that is one dilution higher than the broth method, these six isolates may not truly be penicillin-resistant. The Medical Officer will have to determine if enough evidence exist to approve a penicillin-resistant claim in CAP without these isolates. There were 15 penicillin-resistant *S. pneumoniae* isolates from the sinusitis studies. The changes needed in the microbiology labeling should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 48-55.

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

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

Addendum to Original Review to Include Data submitted in 4 Month Safety Update

NDA#: 21-277

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	06-MAR-01
CDER DATE:	08-MAR-01
REVIEW ASSIGN DATE:	10-MAR-01
REVIEW COMPLETE DATE:	27-MAR-01

SPONSOR: Bayer Pharmaceutical Division
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

CONTACT PERSON: Andrew S. Verderame
Associate Director Regulatory Affairs
Phone Number: (203) 812-5172

SUBMISSION REVIEWED: Data on Penicillin-Resistant *Streptococcus pneumoniae* in Community Acquired Pneumonia (6 additional isolates)

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

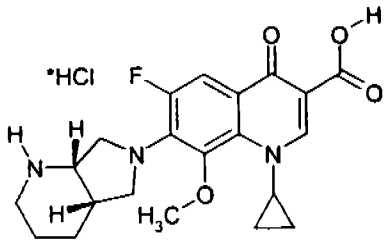
INDICATIONS: Community-acquired pneumonia (CAP), acute sinusitis, and acute bacterial exacerbations of chronic bronchitis (ABECB)

DOSAGE FORM: 400 mg intravenous solution

DRUG PRODUCT NAME

PROPRIETARY: Avelox™
NONPROPRIETARY/USAN: Moxifloxacin Hydrochloride
CODE: BAY 12-8039
CHEMICAL NAME: (1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo(4.3.0)non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolone carboxylic acid hydrochloride

STRUCTURAL FORMULA:



Molecular Formula: $C_{21}H_{24}FN_3O_4 \bullet HCl$
Molecular Weight: 437.9

SUPPORTING DOCUMENTS:

NDA #21-085—Moxifloxacin Tablets (approved 12/10/99)

REMARKS/COMMENTS:

In this submission Bayer provides a microbiology summary of moxifloxacin for the indication of Community Acquired Pneumonia (CAP) due to penicillin-resistant *Streptococcus pneumoniae* (PRSP). Bayer included several literature references regarding the correlation between the MIC measurements by E-test and by broth microdilution testing. A summary of PRSP cases that were treated with moxifloxacin during the moxifloxacin tablet and IV development programs has been provided. An additional six cases of PRSP have been identified from the ongoing 100224 study entitled: "Prospective, non-comparative, open-label, multicenter, multinational trial to evaluate the safety and effectiveness of moxifloxacin oral tablets, 400 mg once daily for 10 days in the treatment of patients with drug resistant *Streptococcus pneumoniae* in community acquired pneumonia."

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY subsection of the package insert. These revisions are listed as notification to the sponsor at the end of this review on pages 17-24.

This submission adds six more isolates of PRSP that were treated with moxifloxacin in CAP studies. Combining the I.V. and Tablet community-acquired pneumonia studies (CAP) there were 19 penicillin-resistant (MIC ≥2 µg/mL) *Streptococcus pneumoniae* isolates according to the sponsor. Seven of these isolates, however, had penicillin susceptibility determined only by the E-test method. These isolates were all from centers outside of the United States and the penicillin MIC could not be determined by broth dilution. Six of the seven had penicillin-MICs of 1.5 or 2.0 µg/mL. Since the E-test method may give a MIC that is one dilution higher than the broth method, these six isolates may not truly be penicillin-resistant.

Bayer has included several literature references to try and show that the E-test method is equivalent to the broth dilution method in determining penicillin resistance in *Streptococcus pneumoniae*. These studies indicate that the results obtained by the two methods are usually within one doubling dilution of each other (equivalent to the error of the assay) for over 90% of the isolates tested, which indicates that the two methods may be considered equivalent. All of the studies, however, indicate that there may be many minor errors (susceptible or resistant by one method and intermediate by the other method). This means that isolates tested by E-test methods that have MICs close to the penicillin resistant breakpoint criteria (≥2 µg/mL) might actually be in the intermediate range and not truly resistant. If these six isolates are not allowed there are 12 isolates with broth dilution MIC results and one isolate with an E-test result of 6.0 µg/mL that can be considered to be truly penicillin resistant. The Medical Officer will have to determine if enough evidence exist to approve a penicillin-resistant claim in CAP without these isolates. There were 15 penicillin-resistant *S. pneumoniae* isolates from the sinusitis studies.

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EXECUTIVE SUMMARY

Moxifloxacin hydrochloride tablets NDA 21-085 was approved in December 1999, for acute sinusitis, community-acquired pneumonia, and acute bacterial exacerbations of chronic bronchitis. This application is for a new formulation of moxifloxacin. This application provides data to show that the two dosage forms are bioequivalent. Two new community-acquired pneumonia clinical trials are included in this application. The sponsor wishes to include patients with severe pneumonia in their indication for CAP. They have also proposed that *Staphylococcus aureus, Klebsiella pneumoniae,* and *Legionella pneumophila* be added to the CAP indication. In addition the sponsor wishes to add penicillin-resistant *Streptococcus pneumoniae* to the sinusitis and CAP indications.

In this safety update Bayer has added six more isolates of penicillin-resistant *Streptococcus pneumonia* from community acquired pneumonia study 100224. All these isolates were tested for penicillin susceptibility by the reference broth microdilution method.

This submission contains several literature studies comparing the E-test method and broth microdilution methods for the determination of penicillin susceptibility in *Streptococcus pneumoniae*. All the submitted studies indicate that over 90% of the MIC values are within one dilution of each other when tested by the two methods. These studies do indicate, however, that there may be many minor errors. These errors include those in which an isolate that is classified as intermediate by the broth dilution method is classified as resistant by the E-test method. Since the broth microdilution method is the reference method, these penicillin-resistant isolates (by E-test method) may not truly be penicillin-resistant.

If only isolates with broth microdilution results are accepted along with isolates tested by the E-test method with penicillin MICs that are not around the resistant breakpoint of 2.0 µg/mL then there are 13 penicillin-resistant *Streptococcus pneumoniae* isolates from community acquired pneumonia studies. Twelve of the thirteen isolates were presumed eradicated. The isolate with an E-test penicillin MIC of 6.0 µg/mL was from a patient who was not cured and the isolate was presumed to be persistent.

SUMMARY OF MICROBIOLOGY OF MOXIFLOXACIN/ COMMUNITY ACQUIRED PNEUMONIA PRSP

OVERVIEW OF PROTOCOL OF STUDY 100224 FOR CAP

This study was a prospective, uncontrolled, multi-national, multi-center clinical trial in which the safety and efficacy of oral moxifloxacin 400 mg tablets once daily for 10 days were evaluated in the treatment of adult patients with community-acquired pneumonia (CAP) associated with penicillin-resistant and macrolide-resistant strains of *Streptococcus pneumonia*.

Patients were screened for enrollment in the trial if they presented with clinical signs and symptoms of community-acquired pneumonia accompanied by radiographic confirmation of an acute infiltrate. In addition, a pre-enrollment sputum Gram stain, which showed at least 25 polymorphonuclear (PMN) leukocytes per high power field and <10 squamous epithelial cells per high power field and which also showed at least one pair of Gram-positive diplococci was required.

The primary population of interest was bacteriologically confirmed cases of CAP associated with penicillin- or macrolide-resistant strains of *S. pneumoniae*. The case definition of a bacteriologically confirmed case was a patient with clinical documentation and radiographic confirmation of an acute infiltrate who also had penicillin- or macrolide-resistant *S. pneumoniae* identified by culture either from a sputum specimen or from pre-therapy blood cultures.

During this clinical study the susceptibility of the causative organisms was determined at the clinical trial sites by the E-test (AB Biodisk). Mueller-Hinton agar supplemented with 5% sheep blood was employed for testing *S. pneumoniae*.

Trial sites sent the clinical isolates to the microbiology laboratory at Bayer Corporation, Pharmaceutical Division for confirmation of each isolate's identity and for susceptibility testing by the broth microdilution test. Susceptibility by the E-test method was also performed. Mueller-Hinton broth supplemented with 2.5% lysed horse blood was used to test *S. pneumoniae*. All broth microdilution tests were performed according to NCCLS guidelines. Quality control strains were included on each day of testing.

There were 23 patients in this study who were microbiologically valid for efficacy who had *S. pneumoniae* as the causative organism. As shown in Table 1 the range of MICs of moxifloxacin for isolates of *S. pneumoniae* in this study was [redacted]. The MIC_{90} was 0.25 µg/mL. These MIC values are the same as those seen in previous studies.

TABLE 1
Moxifloxacin MICs for Pre-Therapy Isolates of All *S. pneumoniae*

Study	No.	Range	MIC_{50}	MIC_{90}
100224	23	0.06-0.25	0.125	0.25

As seen in Table 2 all 23 patients had a clinical response of resolution and all but one patient (22/23) had a bacteriological response of eradication or presumed eradication. Patient 1017 had a bacteriological response of persistence.

TABLE 2
Bacteriological and Clinical Response for All *S. pneumoniae*

Bacteriologic Response (%)			Clinical Response (%)	
Erad	Pres Erad	Persist	Resolve	Fail
2 (8.7	20 (87)	1 (4.3)	23 (100)	0

Three of the viable organisms received by Bayer were isolated from bacteremic patients (patients 1004, 1032, 14011). *Streptococcus pneumoniae* was cultured from blood and sputum from two of three patients and from blood only in one of these three patients. All three patients had a clinical response of resolution and a bacteriological response of presumed eradication. The blood only isolate was penicillin-resistant.

There were six isolates of *S. pneumoniae* that were resistant to penicillin (MICs of 2.0 to 4.0 µg/mL). These isolates were from the sputum of patients 1012, 1019, 1028, 1032, and 604001 and from blood of patient 614002 (TABLE 3). The responses for these six isolates at the Test-of-Cure visit were all resolution and presumed eradication.

TABLE 3
Penicillin MICs of Penicillin-Resistant *S. pneumoniae*
Isolated from CAP Study 100224[a]

Site Number / Country	Patient Number	Source	Broth MIC	Etest MIC
1 / USA	1012	Sputum	2.0	3.0
1 / USA	1019	Sputum	4.0	8.0
1 / USA	1028	Sputum	4.0	3.0
1 / USA	1032	Sputum	2.0	1.5
604 / Spain	604001	Sputum	2.0	2.0
614 / Spain	614002	Blood	2.0	1.0

[a] Enrichment study for isolation of *S pneumoniae*

A REVIEW OF PEN-R *S. PNEUMONIAE* ISOLATED DURING PREVIOUS CAP TRIALS

According to Bayer a total of 13 penicillin-resistant isolates of *Streptococcus pneumoniae* were recovered pre-therapy during clinical studies of community acquired pneumonia (CAP). North American studies accounted for 6 of these 13 isolates (TABLE 4). The studies were 100039 IV (n=4), D96-025 Tablet (n=1), and D96-026 Tablet (n=1). Five of the isolates were cultured from sputum, while the sixth isolate was recovered from both sputum and blood. The clinical response at the Test-of-Cure visit was resolution and all 6 organisms were presumed eradicated.

Penicillin susceptibility testing of these six North American isolates was performed concomitantly by E-test and broth microdilution at the Bayer laboratory. The two methods gave results that were comparable, but the E-test sometimes gave results that were slightly lower or higher than the broth dilution method.

TABLE 4
Penicillin MICs for PEN-R *S. pneumoniae* from CAP[a]

Study Number	Patient Number	Broth MIC	Etest MIC
North America			
100039	13007	2.0	3.0
	13025	4.0	4.0
	48013[b]	2.0	1.5
	71001	4.0	3.0
D96-025	4006	2.0	2.0
D96-026	248	4.0	4.0
Ex North America			
140	10011[c]	---	2.0
	10099	---	1.5
	10370	---	1.5
	10304	---	2.0
	10434	---	2.0
	10674[c]	---	6.0
200036	38101	---	2.0

[a] Isolates submitted in IV CAP NDA
[b] Blood and Sputum Isolates
[c] Patient failure

The other seven of the thirteen penicillin-resistant isolates were from studies outside of North America. These isolates were from study 0140 Tablet (France, n=2; Mexico, n=1; Hong Kong, n=1; Russia, n=1; Spain, n=1) and study 200036 IV (Spain, n=1). All seven isolates were cultured from sputum and susceptibility testing of penicillin was performed by the E-test method only because the Bayer laboratory did not receive the isolates. Table 4 presents the MIC data from these Ex-North American studies. MICs of penicillin were 1.5 µg/mL for two isolates, 2 µg/mL for four isolates, and 6 µg/mL for one isolate. One patient (10011), whose pneumococcal MIC of penicillin was 2 µg/mL, was a clinical failure and the organism was presumed persistent. The penicillin MIC for the other clinical failure (10674) was 6 µg/mL and the bacteriological response was presumed persistence. The remaining 5/7 patients were clinical cures and the bacteriological responses were presumed eradication.

PENICILLIN SUSCEPTIBILITY TESTING BY E-TEST

As noted in the previous section, penicillin MICs were determined by E-test only in the Ex-North America IV CAP studies 140 and 200036 (see TABLE 4). The E-test strip is composed of a predefined exponential gradient of antibiotic, which has been dried, stabilized, and immobilized on one surface of the strip. The resulting continuous antibiotic gradient corresponds to 15 two-fold dilutions used in conventional MIC methods. Broth microdilution tests produce MIC values based on $\log_2$ serial dilutions. E-test MICs are measured in 0.5 $\log_2$ concentrations, therefore, an MIC value may be between two of the usual $\log_2$ dilutions. MICs of 1.5, 3.0 and 6.0 µg/mL are possible with the E-test method.

The penicillin E-test was cleared by the FDA Center for Devices and Radiological Health in 1991 (1,2). In 1994, the FDA recalled all commercial antibiotic susceptibility test systems because of concern that these devices failed to accurately categorize pneumococcal resistance to penicillin (and enterococcal resistance to vancomycin and ampicillin). AB Biodisk E-test, however, was exempted because the performance of penicillin E-test strips for detection of resistant pneumococci was adequately demonstrated in the original filing (3). At FDA's request an evaluation study at the Center for Disease Control (CDC) was performed to reconfirm the effectiveness of the E-test in detecting pneumococcal resistance. The raw data from this study (4) are presented in Table 5. A total of 55 isolates comprised the challenge set for evaluating the penicillin E-test MICs.

TABLE 5
CDC/FDA Pneumococcus Study/Raw Data for Penicillin E-test/Broth Comparison[a]

Isolate #	Broth MIC	Etest MIC		Isolate #	Broth MIC	Etest MIC
1196	0.015	0.03		68	2	2
991	0.03	0.03		195	2	1.5
1100	0.03	0.03		1199	2	3
1499	0.03	0.047		1325	2	1.5
140	0.06	0.09		1825	2	3
1243	0.06	0.06		2562	2	3
1544	0.06	0.06		2570	2	3
1550	0.06	0.047		138	4	2
1683	0.06	0.047		145	4	4
1691	0.06	0.06		146	4	6
1748	0.06	0.06		289	4	6
130	0.12	0.25		1020	4	4
132	0.12	0.12		1293	4	4
133	0.12	0.12		1321	4	6
135	0.12	0.19		1329	4	6
141	0.12	0.25		1346	4	3
152	0.12	0.06		1707	4	4
131	0.25	0.25		1740	4	2
49619	0.25	0.5		2456	4	4
1281	0.5	0.38		2457	4	3
1396	0.5	0.5	↓	2458	4	4
2561	0.5	0.5		2459	4	6
49619	0.5	0.5		110	8	2
49619	0.5	0.5		309	8	24
49619	0.5	0.5		673	8	32
1285	1	1.5	↑	1291	8	16
1427	1	0.5		1426	8	24
2559	1	1		2610	8	6
				121	16	32
				2455	16	32

[a] Raw data for reference Tenover et al. 1996. J Clin Microbiol. 34:10-14.

A comparison of the 25 broth and E-test MIC results around the penicillin-resistant breakpoint of 2.0 µg/mL (1.0-4.0 µg/mL) shows that the penicillin MIC by both methods was the same for 8 isolates (TABLE 6). The E-test MICs for two isolates were 1 $\log_2$ lower than the broth MIC. The E-test MICs for 5 isolates were 0.5 $\log_2$ less than the broth MICs, while E-test MICs for 10 isolates were 0.5 $\log_2$ higher the corresponding broth MICs. One of these 10 isolates had an E-test MIC of 1.5 µg/mL (considered resistant) but a broth MIC of 1.0 µg/mL (intermediate).

TABLE 6
E-test MIC log_2 Difference from Broth Microdilution
MICs around the Penicillin Resistance Breakpoint of 2µg/mL[a]

– 1	– 0.5	=	+ 0.5	+ 1
2	5	8	10	0

[a] Data from Table 5; Broth penicillin MICs of 1, 2, 4 µg/mL; n=25

Bayer has submitted other literature studies that compared penicillin E-test MICs with those produced by the reference NCCLS broth microdilution method (5-10). No very major (resistant by broth and susceptible by E-test) or major errors (susceptible by broth and resistant by the E-test) were observed in any of these studies. There were, however, numerous minor errors (Susceptible by broth, intermediate by E-test; intermediate by broth, susceptible by E-test; intermediate by broth, resistant by E-test; and resistant by broth, intermediate by E-test).

In a study by Jorgensen et al. (5) 147 pneumococcal clinical isolates including 42 penicillin-resistant isolates were tested by the two methods. Penicillin MICs agreed within one log_2 dilution for 136 of 147 (92.5%) of the isolates. There were 9.5% minor errors, however. The majority of these errors (10 or 14) occurred with isolates that were defined as intermediate by broth but were susceptible by the E-test.

A study by Krisher et al. (6) produced 91% agreement within one log_2 dilution with an 18% minor error rate. Only isolates that were intermediate or resistant by the broth method were compared in this study. There were 34 isolates compared and 10 isolates gave E-test results lower than the broth result and 3 isolates gave E-test results higher than the broth results.

In a study by Macias et al. (7) discordant results occurred for 19 of the 108 isolates tested. The E-test interpreted three isolates categorized as resistant to penicillin by broth microdilution as intermediate. All of the discrepancies represented differences of one dilution and occurred at the breakpoint between 2.0 and 1.0 µg/mL. There were five discrepancies for isolates categorized as intermediately resistant by broth. All five isolates were classified as highly resistant by the E-test. None of the isolates classified as intermediate by broth were classified as susceptible by E-test. Eleven of the 49 isolates categorized as susceptible to penicillin by broth were interpreted as intermediate by the E-test.

Skulnick et al. (8) compared both methods against 124 isolates of *S. pneumoniae*. There were 17.6% minor errors. Most of these errors were due to classifying intermediate isolates as resistant by the E-test (14.8%).

Keska et al. (9) reported 97% agreement within one dilution by the two methods. They found a total of 14 (12.4%) minor errors. Six resistant isolates were classified as intermediate by the E-test and one intermediate isolate classified as resistant by the E-test.

Gerardo et al. (10) tested 161 *S. pneumoniae* isolates by both methods. Results were within one dilution for 94.3% of the isolates tested. There was a 1.4% minor error rate. There were only two resistant strains tested in this study. There were 33 isolates with an E-test result that was one dilution higher than the broth test result and only 10 isolates with an E-test result one dilution less than the broth result.

Although there were no very major or major errors found when the E-test method was compared to the reference broth microdilution method for testing penicillin susceptibility to *Streptococcus pneumoniae*, there were numerous minor errors. This means that an isolate that is classified as resistant by the E-test may truly be intermediate by the reference method. This is often the case when the MIC is close to the resistant breakpoint of 2.0 µg/mL. All of the studies submitted indicate that results are within one dilution of each other for over 90% of the isolates tested. All of the studies, however, indicated that minor errors often do occur. Some of these minor errors occur when isolates that should be classified as intermediate are classified as resistant by the E-test method. This often occurs when the MIC is around the penicillin resistant breakpoint of 2.0 µg/mL. The majority of the penicillin-resistant *Streptococcus pneumoniae* isolates in this submission have penicillin MICs of 2.0 µg/mL. These isolates will only be considered to be penicillin-resistant if results from the reference broth microdilution method indicate penicillin MIC ≥2 µg/mL. The only isolate that will be accepted with E-test only results will be the isolate from patient 10674 with an E-test penicillin MIC of 6.0 µg/mL. There are, therefore, 13 penicillin-resistant *Streptococcus pneumoniae* isolates that were cultured from CAP studies.

CLINICAL SUMMARY OF PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* (PRSP)

Moxifloxacin has good activity against *Streptococcus pneumoniae* both *in vitro* and *in vivo*. Table 7 summarizes the clinical success rates seen against *S. pneumoniae* for all IV and Tablet moxifloxacin CAP studies. The overall clinical success rate was 91% (149/164) across all studies.

TABLE 7
Clinical Success Rates against *S. pnuemoniae* across All Moxifloxacin Tablet and Sequential IV/Tablet Studies in CAP

Moxifloxacin Regimen	Study	Moxifloxacin 400 mg	Control
PO	D96-026	17/17 (100%)	18/19 (95%)
PO	D96-025	13/14 (93%)	N/A
PO	0119	14/16 (88%)	12/13 (92%)
PO	0140	34/41 (83%)	35/42 (83%)
PO	100224[a]	23/23 (100%)	N/A
IV/PO	100039	30/35 (86%)	29/33 (88%)
IV/PO	200036	18/18 (100%)	17/22 (77%)
All CAP studies	Uncontrolled Studies	36/37(97%)	
	Controlled Studies	113/127(89%)	111/129 (86%)
	All Studies	149/164(91%)	111/129 (86%)

a. Study is ongoing. Data from this study have not been previously submitted to the agency.

In the subset of patients with *S. pneumoniae* bacteremia in the moxifloxacin studies the clinical success rate was 30/34 (88%) [see Table 8]. The overall clinical success rate in bacteremic patients was 88%. Although the overall moxifloxacin success rate was lower than the success rate of 97% for the control patients, the difference was primarily due to the abnormally low response rate in the 0140 study. The reason for this low rate in Study 0140 is not known.

TABLE 8
Clinical Success Rates in CAP patients with *S. pneumoniae* bacteremia from All Tablet and IV Moxifloxacin Community Acquired Pneumonia Trials

Study	Moxifloxacin 400 mg	Control
PO Moxifloxacin Studies		
Study 0119	1/1 (100%)	1/1
Study 0140	6/9 (67%)	10/10
Study 100224[a]	3/3 (100%)	N/A
IV Moxifloxacin Studies		
100039	9/10 (90%)	11/11 (100%)
200036	11/11 (100%)	9/10 (90%)
All Studies	30/34 (88%)	31/32 (97%)

a. Study is ongoing. Data from this study have not been previously submitted to the agency.

Table 9 summarizes the pooled pathogen eradication rates by penicillin sensitivity of *Streptococcus pneumoniae* at the Test-of-Cure visit in clinically and microbiologically evaluable patients.

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TABLE 9
Pathogen Eradication Rates by Penicillin Sensitivity of
S. pneumoniae at the Test-of-Cure Visit in Moxifloxacin CAP Studies

Study Number	Moxifloxacin 400 mg	Control Regimen[a]
***Streptococcus pneumoniae*, Penicillin Sensitive (MIC < 0.1 µ/ml)**		
Study 100039	23/25 (92%)	26/29(90%)
Study 200036	21/21 (100%)	21/23 (91%)
Study D96-026	13/13 (100%)	14/15 (93%)
Study D96-025	10/10 (100%)	N/A
Study 0140	17/20 (85%)	19/21 (90%)
Study 100224[c]	17/17 (100%)	N/A
All studies	100/106 (95%)	80/88 (91%)
***Streptococcus pneumoniae*, Penicillin Intermediately Resistant (MIC 0.1 - 1 µg/ml)**		
Study 100039	4/6 (67%)	1/2(50%)
Study 200036	4/4 (100%)	1/3 (33%)
Study D96-026	4/4(100%)	1/1 (100%)
Study D96-025	2/3(67%)	N/A
Study 0140	15/17(88%)	10/14 (71%)
Study 100224[c]	-	-
All studies	29/34 (85%)	13/20 (65%)
***Streptococcus pneumoniae*, Penicillin Resistant (MIC ≥ 2 µg/ml)[b]**		
Study 100039	4/4 (100%)	3/3 (100%)
Study 200036	1/1 (100%)	1/2 (50%)
Study D96-026	1/1 (100%)	-
Study D96-025	1/1 (100%)	N/A
Study 0140[b]	4/6 (67%)	1/1 (100%)
Study 100224[c]	6/6 (100%)	N/A
All studies	17/19 (89%)	5/6 (83%)

[a] alatrofloxacin IV/trovafloxacin PO 200/200 mg (initial phase) and IV/PO levofloxacin (continuation phase) in Study 100039, and IV amoxicillin/clavulanate 1.2 g Q8H followed by PO amoxicillin/clavulanate 625 mg Q8H with or without IV/PO clarithromycin in the 200036 Study.
[b] Includes two isolates with a penicillin MIC of 1.5 µg/mL.
[c] This is an ongoing study. Data from this study have not been previously submitted to the agency.

Table 10 shows pooled efficacy data for moxifloxacin from the tablet studies (1040, D96-025, D96-025, 100224) and the sequential IV/Oral moxifloxacin studies (100039 and 200036) in cases of CAP due to PRSP.

Nineteen (19) cases of CAP due to PRSP were identified by Bayer across all moxifloxacin CAP studies. Seven of these 19 isolates were only tested by the E-test method. Six of the seven had MICs of 1.5 to 2.0 µg/mL by E-test. Since the E-test may produce results that are one dilution different than those produced by the reference broth dilution method these six isolates may not actually be penicillin-resistant.

TABLE 10
Clinical and Bacteriological Outcomes with Moxifloxacin 400 mg in Cases of CAP due to Penicillin-Resistant *S. pneumonia*

Study No.	Patient Number	Penicillin MIC (µg/mL)	Clinical Outcome	Bacteriological outcome[b]
D96-026[c]	248	4	Resolved	PE
D96-025[c]	4006	2	Resolved	PE
0140[d]	10011	2	Failed	PE
	10099	1.5	Resolved	E
	10370	1.5	Resolved	PE
	10674	6	Failed	PP
	10304	2	Resolved	PE
	10434	2	Resolved	PE
100224[c]	1012	2	Resolved	PE
	1019	4	Resolved	PE
	1028	4	Resolved	PE
	1032[a]	2	Resolved	PE
	604001	2	Resolved	PE
	614002	2	Resolved	PE
Study 10039[c]	13007	2	Resolved	PE
	13025	4	Resolved	PE
	48013[a]	2	Resolved	PE
	71001	4	Resolved	PE
Study 20036[d]	38101	2	Resolved	PE

a. patient with *S. pneumoniae* isolated from the blood and the sputum
b. PE = presumed eradication, E = eradication, PP = presumed persistence
c. MIC results were determined by broth microdilution
d. MIC results were determined by E-test only. Isolates were not received by Bayer for further testing.

If isolates with only E-test results of 1.5 to 2.0 µg/mL are excluded then there are 13 penicillin-resistant isolates with only the E-test isolate with an MIC of 6.0 µg/mL being a failure.

TABLE 11
Clinical and Bacteriological Outcomes with Moxifloxacin 400 mg
In Cases of CAP due to Penicillin Resistant *S. pneumoniae*
(Excluding Isolates with E-test Results of 1.5 or 2.0 µg/mL)

Study No.	Patient Number	Penicillin MIC (µg/mL)	Clinical Outcome	Bacteriological Outcome[b]
D96-026[c]	248	4	Resolved	PE
D96-025[c]	4006	2	Resolved	PE
0140[d]	10674	6	Failed	PP
100224[c]	1012	2	Resolved	PE
	1019	4	Resolved	PE
	1028	4	Resolved	PE
	1032[a]	2	Resolved	PE
	604001	2	Resolved	PE
	614002	2	Resolved	PE
10039[c]	13007	2	Resolved	PE
	13025	4	Resolved	PE
	48013[a]	2	Resolved	PE
	71001	4	Resolved	PE

[a] Patient with *S. pneumoniae* isolated from the blood and the sputum
[b] PE = presumed eradication; PP = Presumed persistence
[c] MIC results were determined by broth microdilution
[d] MIC results were determined by E-test only. Isolates were not received by Bayer

In summary Bayer has submitted data from 13 isolates of *Streptococcus pneumoniae* which were pathogens in community acquired pneumonia studies that have penicillin MICs obtained by the reference broth microdilution method or which were obtained by the E-test but have a MIC value that is not close to the penicillin resistance breakpoint where a minor error could cause an error in classification. Among these 13 isolates there was only one failure. The Medical Officer will have to decide if this is enough evidence to allow a claim of Community Acquired Pneumonia caused by *Streptococcus pneumoniae* (including penicillin-resistant strains).

If this indication is approved list #1 (clinical efficacy shown) in the Microbiology subsection of the package insert may be revised to include *Streptococcus pneumoniae* (including penicillin-resistant strains) instead of reading *Streptococcus pneumoniae* (penicillin-susceptible strains). *Streptococcus pneumoniae* (penicillin-resistant strains) would then be deleted from list #2 (*in vitro* activity) in the Microbiology subsection.

NDA REFERENCES

1. AB Biodisk. E-test Package Insert; 1997.

2. AB Biodisk. E-test Supplemental Package Insert for Benzylpenicillin; 1998.

3. FDA Center for Devices and Radiological Health. Response to AB Biodisk concerning use of penicillin E-test for determining susceptibility of pneumococci. 1994.

4. Tenover F, Baker C, Swenson J. Evaluation of commercial methods for determining antimicrobial susceptibility of *Streptococcus pneumoniae*. *J Clin Microbiol.* 1996;**34**:10-14.

5. Jorgensen J, Ferraro M, McElmeel M, Spargo J, Swenson J, Tenover F. Detection of penicillin and extended-spectrum cephalosporin resistance among *Streptococcus pneumoniae* clinical isolates by use of the E test. *J Clin Microbiol.* 1994;**32**:159-163.

6. Krisher K, Linscott A. Comparison of three commercial MIC systems, E test, fastidious antimicrobial susceptibility panel, and FOX fastidious panel, for confirmation of penicillin and cephalosporin resistance in *Streptococcus pneumoniae*. *J Clin Microbiol.* 1994;**32**:2242-2245.

7. Macias E, Mason EO, Ocera H, LaRocco M. Comparison of E Test with standard broth microdilution for determining antibiotic susceptibilities for penicillin-resistant strains of *Streptococcus pneumoniae*. *J Clin Microbiol.* 1994;**32**:430-432.

8. Skulnick M, Small G, Lo P, Patel MP, Porter CR, Low DE, Matsumura S, and Mazzulli T. Evaluation of accuracy and reproducibility of E test for susceptibility testing of *Streptococcus pneumoniae* to penicillin, cefotaxime, and ceftriaxone. *J Clin Microbiol.* 1995;**33**:2334-2337.

9. Kiska D, Kerr A, Jones M, Chazotte N, Eskridge B, Miller S, Jordan M, Sheaffer C, and Gilligan P. Comparison of Antimicrobial Susceptibility Methods for Detection of Penicillin-Resistant *Streptococcus pneumoniae*. *J Clin Microbiol.* 1995;**33**:229-232.

10. Gerardo S, Citron D, Claros M, Goldstein E. Comparison of E test to broth microdilution method for testing *Streptococcus pneumoniae* susceptibility to levofloxacin and three macrolides. *Antimicrob Agents Chemother.* 1996;**40**:2413-2415.

RECOMMENDATIONS:

The applicant should be notified of the following:

Assuming that the data submitted is sufficient to approve an indication of uncomplicated skin and skin structure infections:

1. The statement reading "The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, a mechanism of fluoroquinolone resistance" should be revised to read "The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria. The evidence present was related to mechanisms associated with these genes in *S. pneumoniae* and *S. aureus*.

2. The statement reading "*In vitro* resistance to moxifloxacin develops slowly via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency between 1.8×10^{-9} to $<1 \times 10^{-11}$ for Gram-positive bacteria" should be revised to read "*In vitro* resistance to moxifloxacin develops slowly via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency between 1.8×10^{-9} to $<1 \times 10^{-11}$ for Gram-positive bacteria. The mutation rates for Gram-negative bacteria are higher at 1×10^{-8} for *Escherichia coli* and 1×10^{-6} for *Pseudomonas aeruginosa*. This higher mutation rate for *Pseudomonas aeruginosa* is seen with most fluoroquinolones." Mutation rates from Gram-negative bacteria, especially *Pseudomonas aeruginosa* were higher than those for Gram-positive bacteria. This should be reflected in the label.

3. The section of the Microbiology subsection of the label that relates certain pharmacokinetic/pharmacodynamic parameters to clinical efficacy and the included table should be deleted. This information has never been allowed in the labeling before. We usually do not even allow the MIC values to be in the label. Although studies have shown that efficacy seems to be related to these pharmacodynamic parameters the addition of this information in the microbiology section does not really add any useful information since clinical trials have been performed and the drug has been shown to be effective against the organisms listed in the table. Different studies have used slightly different values for the AUC/MIC ratio that leads to efficacy. Most studies seem to indicate that once this value has been reached higher values do not add to the efficacy of the drug. Most studies also have used individual MIC values for each pathogen and not the MIC_{90} value. If this information is allowed into the label it will not really be adding useful information since efficacy against these pathogens has been shown. An AUC/MIC ratio greater than the value needed for good efficacy does not mean the drug has better efficacy against that organism.

4. The addition of penicillin-resistant *Streptococcus pneumoniae* to the clinical efficacy listing will be allowed if enough evidence is provided to show that these isolates are eradicated in the indication of community acquired pneumonia. From the microbiological viewpoint there are 13 penicillin-resistant isolates. Twelve of the thirteen patients were cured and the organism is presumed to be eradicated.

5. The placement of *Streptococcus pyogenes* in the clinical efficacy list (list #1) is acceptable if the skin indication is approved. From the microbiological viewpoint not enough isolates of *Streptococcus agalactiae* were tested in the skin clinical trials to allow this organism into the efficacy list. *Streptococcus agalactiae* may, however, be added to the *in vitro* activity list (list #2) if the skin indication is approved.

6. From the microbiological viewpoint not enough isolates of *Legionella pneumoniae* were studied in the clinical trials to allow this organism into the clinical efficacy list (list #1).

7. *Staphylococcus epidermidis* may be added to the *in vitro* activity listing (list #2) if the skin indication is approved. It should be qualified as (methicillin-susceptible strains only). Although the MIC_{90} values for methicillin-resistant isolates was ≤ 2 µg/mL in all submitted studies, less than 100 methicillin-resistant isolates were tested and the MIC_{90} value was at the susceptible breakpoint. As with other fluoroquinolones the MIC values for methicillin-resistant strains was higher than for methicillin-susceptible strains and methicillin-resistant staphylococci are normally resistant to all fluoroquinolones.

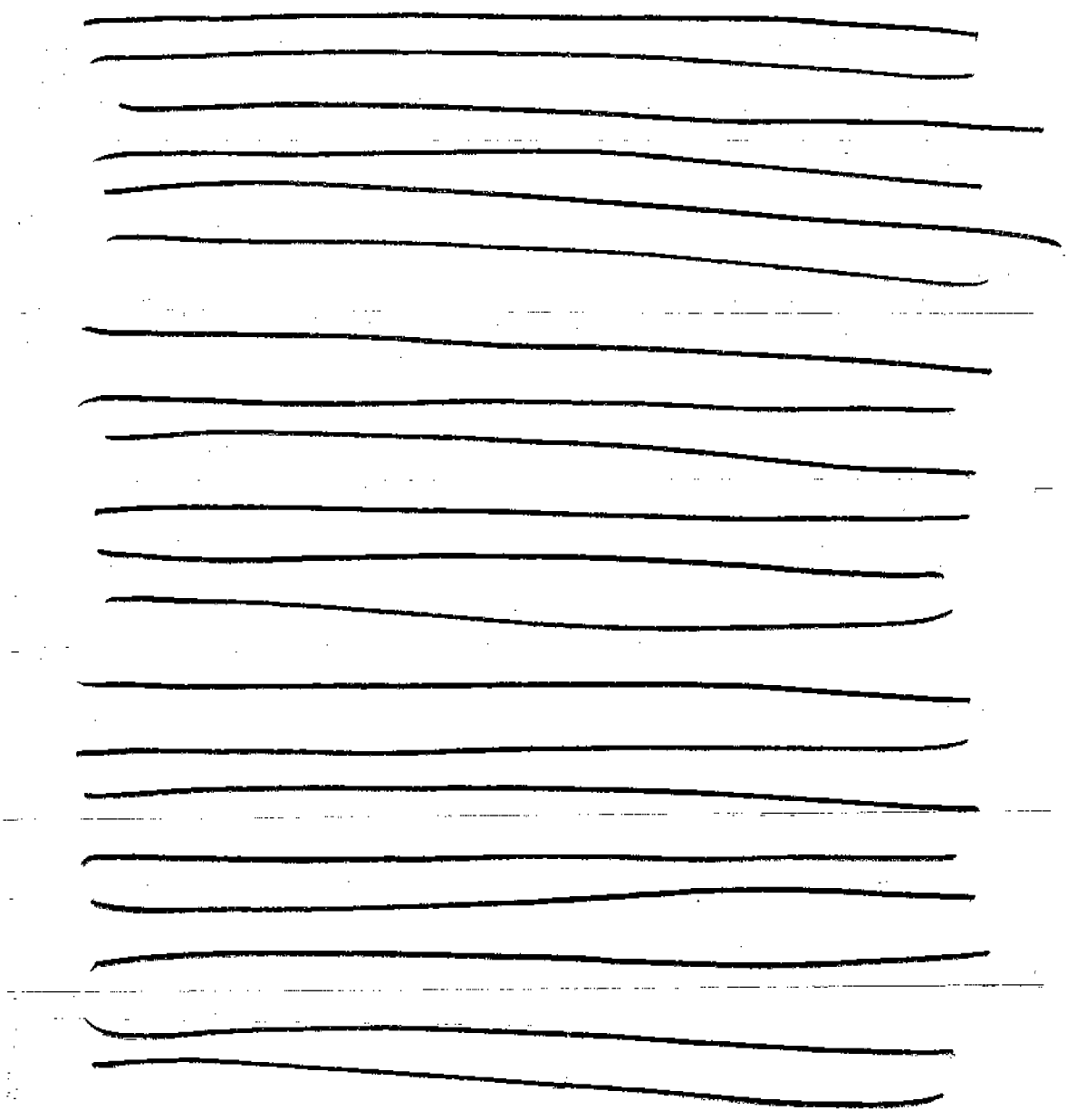
8. *Streptococcus* viridans group and *Streptococcus agalactiae* may be added to the *in vitro* activity listing (list #2) if the skin indication is approved.

9. Since from the microbiological viewpoint not enough isolates of *Legionella pneumophila* were treated in the clinical trials this organism should remain in the *in vitro* activity listing (list #2) instead of being moved to the clinical efficacy list (list #1).

10. In the Susceptibility Tests subsection the words "For testing *Streptococcus* species including *Streptococcus pneumoniae*" should replace the words "For testing *Streptococcus pneumoniae*" in both the Dilution Techniques and the Diffusion Techniques sections.

11. The NCCLS references should be updated to the January 2000 versions.

The Microbiology subsection of the package insert should, therefore, be revised to read as follows: Deletions to the sponsor's proposed labeling are indicated by a strikeout. Additions to the sponsor's proposed labeling are indicated by a double underline.



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

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir_____Signature_____Date
HFD-590/TLMicro_____Signature_____Date

CC:
HFD-590/Original NDA #21-227
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/AMeyerhoff
HFD-520/Pharm/AEllis
HFD-590/Chem/DMatecka
HFD-590/CSO/VJensen

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Peter Dionne
4/16/01 12:51:45 PM
MICROBIOLOGIST

Shukal signed 4/9/01 Ken signed 4/12/01

Shukal Bala
4/16/01 01:21:10 PM
MICROBIOLOGIST

Kenneth Hastings
4/17/01 10:24:01 AM
PHARMACOLOGIST

REVIEW FOR HFD-590
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW # 1 OF NDA

May 09, 2001

A. 1. NDA/ANDA/IND/: NDA 21-277

2. TYPE OF SUPPLEMENT: NA

3. SUPPLEMENT PROVIDES FOR: NA

4. APPLICANT/SPONSOR: Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

5. MANUFACTURING SITE: West Haven, CT

6. DRUG PRODUCT NAME:
Proprietary: Avelox IV®
Nonproprietary: Moxifloxacin hydrochloride I.V. Solution
Drug Priority Classification: 1

6. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: The product is a sterile injectable.

8. METHOD (S) OF STERILIZATION: [redacted]

9. PHARMACOLOGICAL CATEGORY: Antibiotic solution

B. 1. DOCUMENT/LETTER DATE: November 2, 2000

2. RECEIPT DATE: NA – Electronic submission.

3. CONSULT DATE: December 6, 2000

4. DATE OF AMENDMENT: NA

5. ASSIGNED FOR REVIEW: December 7, 2000

6. SUPPORTING/RELATED DOCUMENTS: [redacted]

C. **REMARKS**: The consult requests review of a New Drug Application (NDA 21-277) for MOXI SOL 0.16% 250 mL HCl P (AVELOX™ IV). [redacted] contract manufactures MOXI SOL 0.16% 250 mL HCl P (AVELOX™ IV) in [redacted] Flexible containers for Bayer Corporation. The consult requests a microbiology review of this original NDA 21-277. The microbiological processes were referenced in Drug Master Files [redacted] Drug Master File [redacted] contained the sterilization process validation and container closure validation information specific to this product. Drug master File [redacted] contained the gamma radiation process validation of administrative port assemblies.

D. **CONCLUSIONS**: The Microbiology section of this NDA is recommended for approval based on the information provided.

Vinnie Pawar, Ph.D.

cc:

Original NDA 21-277
HFD 590/Div. File
HFD 160/Consult
HFD 590/Valerie Jensen
HFD 160/Microbiologist/V.Pawar [HFD-805]

Drafted by: V. Pawar, 05/09/2000
R/D initialed by: P. Cooney

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

REVIEW FOR HFD-590
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW # 1 OF NDA

October 17, 2001

A. 1. NDA/ANDA/IND/: NDA 21-277/AC

2. TYPE OF AMENDMENT: AC

3. AMENDMENT PROVIDES FOR: Documentation for Sterilization Process Validation performed at Leverkusen, Germany.

4. APPLICANT/SPONSOR: Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

5. MANUFACTURING SITE: Leverkusen, Germany

6. DRUG PRODUCT NAME:
Proprietary: Avelox IV®
Nonproprietary: Moxifloxacin hydrochloride I.V. Solution
Drug Priority Classification: 1

6. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: The product is a sterile injectable.

8. METHOD (S) OF STERILIZATION: [redacted]

9. PHARMACOLOGICAL CATEGORY: Antibiotic solution

B. 1. DOCUMENT/LETTER DATE: November 2, 2000

2. RECEIPT DATE: NA – Electronic submission.

3. CONSULT DATE: December 6, 2000

4. DATE OF AMENDMENT: July 03, 2001

5. ASSIGNED FOR REVIEW: August 30, 2001

6. SUPPORTING/RELATED DOCUMENTS: [redacted]

C. **REMARKS**: The consult requests review of an amended New Drug Application (NDA 21-277) for MOXI SOL 0.16% 250 mL HCl P (AVELOX™ IV). In the original NDA [redacted] was the contract manufacturer of AVELOX™ IV in [redacted] containers for Bayer Corporation. [redacted] will no longer manufacture this product for Bayer but will continue to provide the container. Bayer will manufacture AVELOX™ IV at Levekusen, Germany. The consult requests a microbiology review of this amended NDA 21-277/AC. The amendment contains documentation for the validation and sterilization activities performed at Leverkusen, Germany facility. Although a hard copy of volume 1 was submitted for review, complete description of the validation process was obtained from the accompanying electronic submission.

D. **CONCLUSIONS**: The Microbiology section of this NDA amendment is recommended for approval based on the information provided.

Vinnie Pawar, Ph.D.

cc:

Original NDA 21-277
HFD 590/Div. File
HFD 160/Consult
HFD 590/Kong Yoon/Valerie Jensen
HFD 160/Microbiologist/V.Pawar [HFD-805]

Drafted by: V. Pawar, 10/17/2001
R/D initialed by: P. Cooney

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