CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-277

ADMINISTRATIVE DOCUMENTS

Section 13: The following information is hereby provided pursuant to 21 C.F.R. § 314.53(c):

Patent Number:	4,670,444
Expiration Date:	30 June 2009 (An application for extension of the patent term to 6 December 2011 was filed with the U.S. Patent and Trademark Office on 28 January 2000.)
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

Patent Number:	5,607,942
Expiration Date:	4 March 2014
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

Patent Number:	5,849,752
Expiration Date:	5 December 2016
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

The undersigned declares that Patent Numbers 4,990,517; 5,607,942; and 5,849,752 cover the formulations, compositions and/or methods of use of moxifloxacin. This product is the subject of this application for which approval is being sought.

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

EXCLUSIVITY SUMMARY for NDA # 21-277
Trade Name: Avelox I.V. Generic Name: moxifloxacin hydrochloride in sodium chloride injection
Applicant Name Bayer Pharmaceutical Corporation HFD-590
Approval Date : November 30, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED ?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

   If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /__X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

   YES /___/ NO /_X__/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product .

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-085 Avelox (moxifloxacin hydrochloride) Tablets

NDA # 21-334 Avelox (moxifloxacin hydrochloride) Tablets (Type 6)

NDA #

2. Combination product **(N/A)**

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /__/

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If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available

from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /__X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__X_/

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 100039

Investigation #2, Study # 200036

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /__X_/
Investigation #2	YES /___/	NO /__X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X__/

Investigation #2 YES /___/ NO /__X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation # 1, Study # 100036

Investigation # 2, Study # 200039

Investigation #__, Study #

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

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

Investigation #1	
IND # _____ YES /_X__/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

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

Investigation #1	
YES /__/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /_X__/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

(see appended electronic signature page)

Yoon Kong, Pharm.D.
Title: Regulatory Project Manager

(see appended electronic signature page)

Renata Albrecht, M.D.
Title: Division Director

cc:
Archival NDA 21-277
HFD-590/Division File
HFD-590/Yoon Kong
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Yoon Kong
11/30/01 04:49:26 PM

Renata Albrecht
11/30/01 05:02:37 PM

Section 16 **Debarment Certification**

Bayer hereby certifies under FD&C Act, Section 306(k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

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

Printable Pediatric Page

Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	021277	**Trade Name:**	AVELOX (MOXIFLOXACIN HCL) IV 400MG
Supplement Number:	000	**Generic Name:**	MOXIFLOXACIN HCL
Stamp date:	11/2/00	**Action Date:**	11/2/00
Supplement Type:	N		
COMIS Indication:	COMMUNITY-ACQUIRED PNEUMONIA/ACUTE SINUSITIS/ACUTE EXACERBATION OF CHRONIC BRONCHITIS		

Indication #1: Acute Bacterial Sinusitis caused by Streptococcus pneumoniae, Haemophilus influenza, or Moraxella catarrhalis - Date Entered: 11/30/01

Status: No ranges entered for this Indication

Add New Range to Indication 1

Indication #2: Acute Bacterial Exacerbation of Chronic Bronchitis caused by Streptococcus pneumoniae, Haemophilus influenza, Haemophilus parainfluenza, Klebsiella pneumoniae, Staphylococcus aureus, or Moraxella catarrhalis - Date Entered: 11/30/01

Status: No ranges entered for this Indication

Add New Range to Indication 2

Indication #3: Community Acquired Pneumonia caused by Streptococcus pneumoniae, Haemophilus influenza, Klebsiella pneumoniae, Staphylococcus aureus, Moraxella catarrhalis, Mycoplasma pneumoniae or Chlamydia pneumoniae - Date Entered: 11/30/01

Status: No ranges entered for this Indication

Add New Range to Indication 3

Indication #4: Uncomplicated Skin/Skin Structure Infections caused by Staphylococcus aureus or Streptococcus pyogenes - Date Entered: 11/30/01

Status: No ranges entered for this Indication

Add New Range to Indication 4

This page was printed on 11/30/01

Signature

11-30-01

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
For: Carl E. Calcagni, RPh	Vice President Regulatory Affairs
FIRM/ORGANIZATION	
Bayer Corporation, Pharmaceutical Division	
SIGNATURE	**DATE**
Arlene A. Kodesmun	November 2, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

NDA 21-277
NDA 21-334

MEMORANDUM

DATE: January 16, 2001

TO: Andrew Verderame
Associate Director, Regulatory Affairs

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

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

SUBJECT: Request for information regarding initial review of NDA 21-277 for Avelox® IV and NDA 21-334 for the resubmission of the uncomplicated skin and skin structure indication to NDA 21-085, Avelox® (moxifloxacin hydrochloride) 400 mg Tablets.

NDA 21-277 for Avelox ® (moxifloxacin hydrochloride) I.V. solution was submitted November 2, 2000 and received on November 3, 2000. NDA 21-334 was submitted on October 26, 2000 and received on October 27, 2000. NDA 21-334 is an administratively-assigned NDA number which involves the resubmission of the uncomplicated skin and skin structure indication to NDA 21-085 for Avelox® (moxifloxacin hydrochloride) 400 mg tablets. NDA 21-085 was approved on December 10, 1999 and the indication of uncomplicated skin and skin stucture infection was given an approvable action on December 10, 1999. We have the following initial review requests regarding NDA 21-277 and NDA 21-334:

Clinical Pharmacology and Biopharmaceutics:

1) Please submit selected pharmacokinetic, pharmacodynamic, and pharmacokinetic/pharmacodynamic data and parameters for clinical Studies 100039 and 200036 electronically in Excel format (see attached sample tables) to assist in review.

2) Please submit the following pharmacodynamic data for Studies 100263, 100264, and 100267 in Excel format to assist in review:
    - Individual QTc-related parameters (see attached sample tables).
    - Table 14.2/5.2.1 [Listing of Bazett QTc (msec) by sampling time] and Table 14.2/5.2.2 [Listing of Fridericia QTc (msec) by sampling time]. For Study 100263 please ensure that both tables contain data from 6 and 12 hour sampling times as well as data from all sampling times on Day -1.

3) Please submit the quality control (QC) data for the analytic method used in generating the pharmacokinetic data for Studies 100263, 100264, and 100267.

4) The pooled analysis using data from Studies 100263, 100264, and 100267 to characterize the pharmacokinetic profile of moxifloxacin and its conjugated metabolites (M1 and M2) in young and elderly adult males and females, after single and multiple 400 mg oral doses, has not been submitted. Please submit this report as soon as possible.

Pharmacology-Toxicology:

We request information on the difference (if any) between reports R 7264 (submitted in the original Avelox tablet NDA, 21-085), and R 7510 (submitted in the Avelox IV NDA, 21-277). Both reports are for a study called "Comparison of QT Prolongation and Arrhythmias in Rabbits Treated with BAY 12-8039 or Sparfloxacin" and the report R 7510 states that it is replacing R 7264.

Please call Valerie Jensen, R.Ph., Project Manager, at (301) 827-2127 if you have any questions related to this correspondence.

Date: June 4, 2001

To: Andrew Verderame
Deputy Director, Regulatory Affairs
Bayer Corporation
Pharmaceutical Division

From: Valerie Jensen, R.Ph.
Regulatory Project Manager

Subject: NDA 21-277

Dear Mr. Verderame:

Please refer to your November 2, 2000 submission of NDA 21-277 for Avelox® IV solution. We have the following questions regarding Study #100039 which was submitted to NDA 21-277.

1. There are datasets presenting ECG findings from 1) [redacted] and 2) [redacted] (dataset [redacted]. Why were two contract research organizations used to read and/or interpret ECG findings in this study?

2. Were all ECGs from all patients read by both CROs?

3. An attempt to identify patients who received moxifloxacin and who had a QT_c interval $\geq$ 0.500 sec at any time after the pre-therapy visit yielded markedly different results from each of these two datasets. These two datasets both contain 1971 records (rows). [redacted] included 17 patients who met this criterion and ECG included 8 such patients. Those 8 patients were not a subset of the 17, but, rather, included some that were among the 17 in [redacted] and some that were not. There is no single database that will provide a complete subset of patients who meet these criteria.

   a) Please explain the difference in results when these two datasets are searched.

   b) Please provide a complete list of those patients enrolled in study #100039 who were found to have a QTc $\geq$ 500 msec at any time after the pretherapy visit. Please present patients by treatment group and include whether or not the ECG was valid.

Please call Valerie Jensen, R.Ph., Regulatory Project Manager at (301) 827-2374 with any questions related to this correspondence.

Date: June 21, 2001

To: Andrew Verderame
Deputy Director, Regulatory Affairs
Bayer Corporation
Pharmaceutical Division

From: Valerie Jensen, R.Ph.
Regulatory Project Manager

Subject: NDA 21-277

Dear Mr. Verderame:

Thank you for your response dated June 12, 2001 regarding reading of ECGs in NDA 21-277, Study #100039. We have undertaken analyses of ECG data using both [redacted] datasets and have the following questions:

1. As initially conveyed to you in our facsimile dated June 4, 2001, when both datasets are queried for patients who are found to have a QT_c measurement $\geq$ 500 msec any time after the pre-infusion visit, the results from the two datasets are quite different. Among those who received moxifloxacin, a total of 17 such patients are identified in the [redacted] dataset, and 8 in th[redacted] dataset. Of the 17 identified in [redacted], 11 were not identified by [redacted]. There were 5 patients who met these outlier criteria who were identified by both contractors. There were 3 patients identified by [redacted] who were not identified by [redacted].

   It is noted from your response dated June 12, 2001, that no comparison was attempted between the interval readings of [redacted] Given the above findings, can you hypothesize a reason for the observed discrepancy?

2. A comparison of the readings obtained by [redacted] for a sample of patients showed that the duration of the QT_c interval reported by [redacted] was at times markedly different than that reported by [redacted] and not explained by carrying out the measurement to 3 decimal places instead of 2. For one patient the measurement reported by [redacted] was 176 msec shorter than that reported by [redacted] for the same patient at the same visit. Please describe the process by which [redacted] was determined to be the definitive reader for study #100039.

3. There does not appear to be an amendment to the protocol for study #100039 describing the change to [redacted] from the previously designated reader [redacted]. Please inform us if such an amendment was submitted, and where it can be found in the NDA submission.

4. An analysis of the adverse events experienced by the outliers described in #1 above was undertaken. One of these outliers, identified only in the query of the [redacted] dataset and not in the query of [redacted] was found to have an event described by the investigator as a "burst of ventricular tachycardia." Please submit the CRF and all ECG tracings for patient number #100039-108-108015.

Please call Valerie Jensen, R.Ph., Regulatory Project Manager at (301) 827-2374 with any questions related to this correspondence.

APPEARS THIS WAY
ON ORIGINAL

Date: June 22, 2001

To: Andrew Verderame
Deputy Director, Regulatory Affairs
Bayer Corporation
Pharmaceutical Division

From: Valerie Jensen, R.Ph.
Regulatory Project Manager

Subject: NDA 21-277

Dear Mr. Verderame:

We have the following request regarding studies #100039 and #200036 submitted to NDA 21-277 for Avelox IV.

Please provide demographic analysis for microbiologically evaluable patients. The analysis should be similar to the analysis for efficacy valid patients for both studies #100039 and #200036.

Please call Valerie Jensen, R.Ph., Regulatory Project Manager at (301) 827-2374 with any questions related to this correspondence.

APPEARS THIS WAY
ON ORIGINAL

Date: June 27, 2001

To: Andrew Verderame
Deputy Director, Regulatory Affairs
Bayer Corporation
Pharmaceutical Division

From: Valerie Jensen, R.Ph.
Regulatory Project Manager

Subject: NDA 21-277

Dear Mr. Verderame:

We have the following questions regarding study #100039 and study #200036 submitted with NDA 21-277 for Avelox IV.

1. Does the version of COSTART used in study #100039 include the term 'torsades de pointes?' Does the version of COSTART used in study #200036 include the term 'torsades de pointes?'

2. We are reviewing the cases of ventricular tachycardia reported from both of these studies. Please provide all ECG tracings documenting ventricular tachycardia for the patients reported to have experienced this arrhythmia. The patients' numbers are provided below:

   100039-023-23009
   100039-050-50008
   100039-079-79082
   100039-108-108015*
   100039-030-30025
   200036-920-69902

   *This patient's ECG tracings were requested earlier. If the tracings documenting ventricular tachycardia have already been forwarded to the Division, please let us know.

Please call Valerie Jensen, R.Ph., Regulatory Project Manager at (301) 827-2374 with any questions related to this correspondence.

Date: July 3, 2001

To: Andrew Verderame
Deputy Director, Regulatory Affairs
Bayer Corporation
Pharmaceutical Division

From: Valerie Jensen, R.Ph.
Regulatory Project Manager

Subject: NDA 21-277

Dear Mr. Verderame:

We have reviewed the case of patient #100039-113-113010 and have the following question:

This patient had a permanent pacemaker and chronic atrial fibrillation. He experienced cerebrovascular ischemia, an event regarded as a surrogate of arrhythmia, and subsequently died. Review of his ECG data showed that his heart rate was consistently recorded at values of approximately 70 beats per minute with evidence of a functioning artificial pacemaker. There are measurements of the QT_c interval for each data point, and for each of these taken after the initiation of moxifloxacin, the patient's QT_c duration is observed to be greater than 500 msec. These ECGs are scored invalid; the reason provided is that the patient was in atrial fibrillation. Please explain why such ECG tracings were considered invalid in a patient who is not tachycardic and with a paced ventricular rhythm that would presumably result in a constant R-R interval.

Please call Valerie Jensen, R.Ph., Regulatory Project Manager at (301) 827-2374 with any questions related to this correspondence.

APPEARS THIS WAY
ON ORIGINAL

Date: July 18, 2001

To: Andrew Verderame
Deputy Director, Regulatory Affairs
Bayer Corporation
Pharmaceutical Division

From: Valerie Jensen, R.Ph.
Regulatory Project Manager

Subject: NDA 21-277

Dear Mr. Verderame:

For Study #100039, please provide summary statistics (minimum, maximum, mean, median, standard deviation, Q1, Q2, Q3) by treatment for the duration between TOC visit and end of therapy for the three analysis populations; the safety, efficacy and microbiologically evaluable populations.
Please provide a data set containing this information.

Please call Valerie Jensen, R.Ph., Regulatory Project Manager at (301) 827-2374 with any questions related to this correspondence.

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELECONFERENENCE

DATE OF TELECONFERENCE:	June 14, 2001
APPLICATION:	NDA 21-277
DRUG:	AVELOX® (moxifloxacin hydrochloride) IV Solution
SPONSOR:	Bayer Corporation Pharmaceutical Division
SUBJECT:	Manufacturing site change for NDA 21-277
BAYER AG, LEVERKUSEN ATTENDEES:	Bernd Kuehn, Manufacturing Ute Lichtenberg, Microbiology/Sterilization Hans-Friedrich Mahler, Quality Assurance Gerd Toppel, Production
BAYER, WEST HAVEN ATTENDEES:	Paula Buckely, Quality Assurance Carl Calcagni, Regulatory Bill Chiarelli, Manufacturing Robin Christoforides, Regulatory Edward Huguenel, Project Management Mary Kuhn, Manufacturing Albert Poierier, Quality Assurance Hans Scholl, Quality Assurance Michael Staschewski, International Project Management Andrew Verderame, Regulatory
FDA ATTENDEES:	Norman Schmuff, Ph.D., Chemistry Team Leader Dorota Matecka, Ph.D., Chemistry Reviewer Vinayak Pawar, Ph.D., Microbiology Reviewer Valerie Jensen, R.Ph., Project Manager

BACKGROUND:
Bayer requested a teleconference with the Division of Special Pathogen and Immunologic Drug Products to discuss their plans to submit an amendment to NDA 21-277 to provide for a new drug product manufacturing facility. Bayer submitted a background package dated June 7, 2001 which contained a summary of Bayer's plans regarding the manufacturing facility change and a list of discussion points to be used to facilitate the teleconference held June 14, 2001. Items discussed during the teleconference are reproduced below.

DISCUSSION:

1. Dr. Pawar asked Bayer what fill line they plan to use. Dr. Pawar asked if the fill line used for Avelox IV is the same fill line used for the product [redacted]

   Bayer confirmed that a different fill line will be used for Avelox IV than the fill line used for [redacted] but that the fill lines for both products are in the same facility.

2. Dr. Matecka asked about the table presented on page 10 of the June 7, 2001 background package. Dr. Matecka asked for further clarification regarding facilities involved in the manufacture of the drug product and drug substance for Avelox IV.

   Bayer responded that the first steps for the drug substance are carried out in Wuppertal, Germany or Leverkusen, Germany and the final step is carried out in Wuppertal, Germany for Avelox IV.

   Dr. Matecka asked if any stability testing is done in the U.S. for Avelox IV.

   Bayer responded that all product testing is done in Leverkusen and then the product is released to Bayer. The identity testing is done in the U.S.

Bayer Discussion Items: (Bayer discussion items and comments appear in bold text below and Division comments appear in regular text.)

1. **Bayer plans to submit 3 months of stability data obtained from three batches manufactured at the Bayer AG Leverkusen facility as primary stability data. In addition, Bayer proposes to use the [redacted] manufactured batches, previously submitted in the Avelox IV NDA as supportive data as noted in Section 8.3.8 (Stability) of this briefing package. Bayer will provide updated 6 months accelerated stability information as soon as it becomes available in August 2001.**

   The Division agreed with this plan.

2. **As discussed in Section 8.2 (Status of Bayer AG Leverkusen Facility), the sterile manufacturing and filling facility was recently inspected by the German Control Agency by Dr. Neuhaus. Dr. Neuhaus is well known to the FDA from recent**

joint inspections in support of Mutual Recognition Inspections. Bayer recognizes the potential for an FDA foreign inspection. Bayer asks the FDA to consider a waiver of the Pre-Approval Inspection in light of the following:

- **Mutual Recognition Inspections as discussed in Section 8.1 and above**
- **Positive FDA inspection history as discussed in Section 8.1**

The Division responded that the Mutual Recognition Agreement on GMP inspection is currently not active; furthermore in 1991 there was a Withhold recommendation for the Leverkusen facility regarding a Large Volume Parenteral (LVP) product inspection. There has not been an acceptable LVP inspection at the Leverkusen facility thus far. Therefore, there should be a pre-approval inspection of this facility.

3. **Bayer acknowledges the review deadline of the Division (September 2, 2001 for a 10 month review). Though the drug product manufacturing site has changed, the reason for changing the vast majority of the associated documents is to only reflect the new site of manufacture and not to change the technical content. Consequently, Bayer respectively requests the FDA to retain a 10 month review action date, if possible.**

   Bayer stated during the teleconference that they plan to submit the CMC amendment to NDA 21-277 on June 28, 2001 containing all updated CMC information except stability. Bayer stated they would prefer that the amendment be considered a major amendment which would extend the 10 month review clock.

   The Division requested that all new CMC information, including stability, be submitted in one CMC amendment. The Division currently plans to take an action on NDA 21-277 in August, 2001. The Division will decide internally once the amendment is received whether the amendment will be able to be reviewed during this review cycle. The Division stated that review of this amendment will involve filing the German facility in our EES database, a European inspection, a new review by our microbiology consultants, and additional CMC review time.

4. **As discussed with Dr. Randy Levin, Bayer proposes to submit a single CD to the central document room to be processed and placed on the FDA network consistent with the original submission and safety update. Desk copies (electronically or hard copy) will be provided pursuant to the Division's request.**

   The Division agreed with this plan and requested 2 hard copy versions to the submission.

5. **As the revisions to the package insert are minor in nature (refer to Section 9.3, Package Insert) Bayer proposes to only include a revised proposed package insert in the CMC amendment. Therefore, Bayer is not planning to include a revised history, current package insert, package insert and annotated package**

insert (documents in Sections 2 and 3 of the NDA) in the electronic submission.

The Division responded that the labeling for NDA 21-277 has not yet been negotiated and will be resolved independently from the CMC amendment issue. The Division agreed with Bayer's plan to provide a revised proposed package insert with the CMC amendment.

6. **In addition to the above, Bayer would like to discuss the possibility of and the data requirements for an option to include the filling of Avelox IV in PVC flexible containers at the Bayer AG, Leverkusen facility (in addition to polyolefin flexible containers.) There is a significant amount of stability data (104 weeks) available for batches made and [redacted] flexible containers. There is no PVC site specific stability data available for the Bayer AG, Leverkusen facility. Based on the significant amount of information available on Avelox IV manufactured at [redacted] Bayer asks the Division to consider the possibility of an amendment with no site specific stability data with a commitment to provide site specific stability data as soon as it becomes available (Q3 – Q4 2001). The PVC flexible containers and overwraps would be provided by [redacted] and subject to Drug Master Files.**

Bayer stated during the teleconference that they no longer wish to use the PVC flexible containers as mentioned above in Discussion item #6. Bayer considered using these containers when they were unclear about production schedules and now are only planning to use the [redacted] containers.

7. **Bayer requested during the teleconference that the Division file the Leverkusen facility now as a manufacturing site for Avelox IV. Bayer AG representatives confirmed that this site is now ready for inspection. Bayer confirmed that the line is currently active and stated that the line will be shut down from August 5, 2001 through August 17, 2001.**

The Division agreed to file the Leverkusen facility and request an inspection at this time.

Signature, minutes preparer:_____ **Date:**_____

Conference Chair:_____ **Date:**_____

Addendum:
Additional requests from Microbiology Consultant.

Requests and comments from Microbiology Consultant:
For the purpose of microbiological review of the planned amendment to NDA 21-277, the following items will be needed (please refer to 1994 Guidance for Industry for Submission of Documentation for Sterilization Process Validation.

1. Sterilization cycles and Release parameters for the new autoclave.
2. Thermal qualification of cycle with heat distribution and heat penetration data (section B).
3. Microbial Efficacy of the cycle (section C).
4. Environmental Monitoring data – filling area (section D).
5. Container/Closure and package Integrity – for the new cycle (section E).
6. Sterility testing (data for Stability Lots) protocol and release criteria (section G).
7. Holding time on bulk prior to filling, upper limit.