CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-334 *and* 21-085/S-010

ADMINISTRATIVE DOCUMENTS

from NDA 21-085 submission:

Section 13: The following information is hereby provided pursuant to 21 U.S.C. 355(b) and 21 C.F.R. 314.53:

Patent Number:	4,990,517
Expiration Date:	30 June 2009
Type of Patent:	drug, drug product and method of use
Name of patent owner:	Bayer AG
Agent:	applicant (Bayer Corporation) has a place of business in the U.S.

Patent Number:	5,607,942
Expiration Date:	4 March 2014
Type of Patent:	drug, drug product and method of use
Name of patent owner:	Bayer AG
Agent:	applicant (Bayer Corporation) has a place of business in the U.S.

The undersigned declares that Patent Nos. 4,990,517 and 5,607,942 each cover the formulation, composition, and/or method 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
Pharmaceutical Division
Bayer Corporation

EXCLUSIVITY SUMMARY for NDA # 21-334 SUPPL # _____

Trade Name Avelox Generic Name Moxifloxacin HCl

Applicant Name Bayer Corporation HFD- 590

Approval Date 4/27/01

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:

This application is a resubmission (Class II resubmission) of the Uncomplicated Skin and Skin Structure Infections (USSSI) indication for Avelox Tablets. The original NDA for Avelox Tablets (NDA 21-085) was approved 12/10/99 and the

indication of USSSI was given an approvable action in the 12/10/99 AP letter.

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 # Avelox Tablets 400 mg 21-085

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

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: _____

_____

(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 # 0158/D97-005

Investigation #2, Study # 0131

Investigation #3, Study # PMOS study (250991)

Investigation #4, Study # ACES study (100268)

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 /_X_/

Investigation #4 YES /___/ NO /_X_/

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 /_X_/

Investigation #4 YES /___/ NO /_X_/

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 # 0158/D97-005

Investigation #_2_, Study # 0131

Investigation #_3_, Study # PMOS study (250991)

Investigation # 4, Study # ACES study (100268)

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

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

Investigation #1 IND # [redacted]	YES /_X_/	NO/__/ Explain:
Investigation #2 IND # _____	YES /___/	NO /_X/ Explain: This study was not done under an IND (was done outside the US.)
Investigation #3 IND # _____	YES /___/	NO /_X_/ Explain: This study was not done under an IND (was an active surveillance study done under NDA 21-085.
Investigation #4 IND # _____	YES /___/	NO /_X_/ Explain: This study was not done under an IND (was an active surveillance study done under NDA 21-085.

(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 #2 YES/__X__/Explain: Study funded by Bayer.	
Investigation #3 YES /__X__/ Explain Study funded by Bayer and done under NDA 21-085	NO /___/ Explain _____
Investigation #4 YES X__/ Explain Study funded by Bayer and done under NDA 21-085	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: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
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

Debarment Certification

Bayer certifies under the FD&C Act, Section306(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*.

for A.W. Rochfort

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

* Includes clinical investigators from Studies 100263, 100264, 100267, 100268 (US Observational Study, submitted Sept. 28, 2000), and the German Observational study (submitted Sept. 18, 2000). We also certify that the members of the Critical Events Committee, who independently reviewed and provided expert assessment of the US and German observational studies, have not been debarred. In addition, we certify that Bayer staff that compiled the "One million patient report" (submitted on Sept. 19, 2000) have not been debarred.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21085	**Trade Name:**	AVELOX (MOXIFLOXACIN HCL)
Supplement Number:		**Generic Name:**	MOXIFLOXACIN HCL
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	Community Acquired Pneumonia Uncomplicated Skin Infection Acute Exacerbation of Chronic Bronchitis Sinusitis

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, VALERIE JENSEN

Signature /S/ Date 11/9/99.

(from NDA 21-085)

Pediatric Waiver Request:

Bayer hereby requests a waiver from the conduct of pediatric studies for this NDA. Cartilage lesions have been demonstrated in the weight bearing joints of immature dogs given moxifloxacin. This is a class effect of quinolones. The Warnings section of the proposed package insert cautions against the use of this product in pediatric patients and in adolescents (less than 18 years of age).

Although Bayer Corp. does not believe this effect translates itself into human pathology, Bayer believes that it is necessary to get additional experience on moxifloxacin in adults prior to performing pediatric studies.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021334
Trade Name: AVELOX (MOXIFLOXACIN HCL) 400MG TABLETS
Generic Name: MOXIFLOXACIN HCL
Supplement Number: 000 **Supplement Type**: N
Dosage Form:
Regulatory Action: AE **Action Date**: 12/10/99
COMIS Indication: UNCOMPLICATED SKIN/SKIN STRUCTURE INFECTIONS

Indication #1: Uncomplicated Skin and Skin Structure Infections (USSSI)
Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any) Please see NDA 21-085 (indication of USSSI was given approvable action when this NDA was approved.) 21-334 is a resubmission of USSSI indication. Pediatric studies were waived for 21-085.

Lower Range	Upper Range	Status	Date
0 years	18 years	Waived	4/27/01

Comments: Please see action pkg. for NDA 21-085. Reasons cited for waiver are no meaningful therapeutic benefit for pediatric pop., numbers of pediatric patients who would use the drug very small, and safety concerns.

This page was last edited on 4/20/01

Signature /S/ Date 6/11/01

[redacted]
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 [redacted] NDA 21-334 for the resubmission of the uncomplicated skin and skin structure indication to NDA 21-085, Avelox® (moxifloxacin hydrochloride) 400 mg Tablets.

[redacted] 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 [redacted] 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.

[redacted]
NDA 21-334

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), [redacted] 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.

APPEARS THIS WAY
ON ORIGINAL