

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-404

21-405

21-061/s010, s016

21-062/s011, s017

**ADMINISTRATIVE / CORRESPONDENCE
DOCUMENTS**

From December 28, 1998
Submission to NDA 21-061

PATENT INFORMATION

Patent No.: 4,980,470
Expiration Date: December 25, 2007
Type of Patent: Drug
Patent Owner: Kyorin Pharmaceutical Co., Ltd.

Bristol-Myers Squibb Company is the exclusive licensee of U.S. Patent No. 4,980,470.

DECLARATION

The undersigned declares that U.S. Patent No. 4,980,470 covers the drug substance for which approval is being sought in this NDA.

David M. Morse
Signature of authorized person

David M. Morse

Name of authorized person

Patent Counsel - Wallingford

Title of authorized person

September 16, 1998

Date

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: NDA 21-404 and NDA 21-405 (NOTE: The USSSI indication for Tequin was "approvabled" in the December 17, 1999 approval letter for NDAs 21-061 and 21-062. The June 29, 2001 resubmissions for the USSSI indication were assigned NDA numbers 21-404 and 21-405 for the Division's administrative purposes.)

Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: June 29, 2001 (for both NDAs 21-404 and 21-405) Action Date: October 17, 2002 (for both NDAs)

HFD -590 Trade and generic names/dosage form: Tequin (gatifloxacin HCl) Tablets (NDA 21-404) and Tequin (gatifloxacin HCl) Injection (NDA 21-405)

Applicant: Bristol-Myers Squibb Company Therapeutic Class: 4030100 (antibacterial - quinolone)

Indications previously approved (under NDAs 21-061 and 21-062 {NDAs 21-404 and 21-405 are Type 6 NDAs}); community-acquired pneumonia, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis (AECB), uncomplicated urinary tract infections, complicated urinary tract infections and pyelonephritis, uncomplicated gonorrhea

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for these applications: 1

Indication #1: uncomplicated skin and skin structure infections

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver X Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. 0 yr. 0 Tanner Stage _____
Max _____ kg _____ mo. 0 yr. 16 Tanner Stage _____

Reasons for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): January 2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi

HFD-960/Grace Carmouze

(revised 9-24-02)

FOR QUESTIONS ON COMPLETING

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

/s/

Diana Willard
6/5/03 08:20:10 AM

EXCLUSIVITY SUMMARY for NDAs 21-404 and 21-405

Trade Name Tequin Tablets (NDA 21-404) Generic Name gatifloxacin HCl
Tequin Injection (NDA 21-405)

Applicant Name Bristol-Meyers Squibb HFD-590

Approval Date October 17, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

If yes, what type? SE1

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 / / NO / /

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

NDA # 21-061 (Tequin {gatifloxacin HCl} Tablets)

NDA # 21-062 (Tequin {gatifloxacin HCl} Injection)

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES / 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 # AI420-005

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO / X /

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

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 /___/

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 # AI420-005

Investigation #__, Study #

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.

- (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 # 52,081 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 /___/ 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: _____

Signature of Preparer
Title:

Date

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

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

/s/

Diana Willard
12/16/02 09:38:44 AM

Renata Albrecht
12/17/02 05:44:28 PM

USER FEE VALIDATION SHEET

NDA # 21-405 Supp. Type & # _____ UFID # _____
 (e.g., N000, SLR001, SE1001, etc.)

1. YES NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

no User Fee Cover Sheet submitted - it had been requested
Note: this is a Class 2 Resubmission that the Division administrc-
tively assigned an NDA # to.

2. YES NO APPLICATION CONTAINS CLINICAL DATA?
 (Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).)

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION. NDA 21-062

3. YES NO SMALL BUSINESS EXEMPTION

4. YES NO WAIVER GRANTED

5. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other than bundling).
 If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division	Fee	No Fee
N _____	HFD- _____	Fee	No Fee
N _____	HFD- _____	Fee	No Fee

6. YES NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
 (Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).)

NDA #	Division	NDA #	Division
N _____	HFD- _____	N _____	HFD- _____

7. P S PRIORITY or STANDARD APPLICATION? This is resubmission.
N/A

Diana M Willard 8/6/01
 PM Signature / Date

Ellen C. Frank 6 Aug 01
 CPMS Concurrence Signature / Date

USER FEE VALIDATION SHEET

NDA # 21-404 Supp. Type & # _____ UFID # _____
(e.g., N000, SLR001, SE1001, etc.)

1. YES NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

no User Fee Cover sheet submitted - it has been requested
Note: this is a Class 2 Resubmission that the Division administ
tively assigned an NDA # to

2. YES NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION. NDA 21-061

3. YES NO SMALL BUSINESS EXEMPTION

4. YES NO WAIVER GRANTED

5. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other than bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division	Fee	No Fee
N _____	HFD- _____	Fee	No Fee
N _____	HFD- _____	Fee	No Fee

6. YES NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N _____	HFD- _____	N _____	HFD- _____

7. P S PRIORITY or STANDARD APPLICATION? N/A This is resubmission
N/A

Diana M. Willard 8/6/01
PM Signature / Date

Evenc. Frank 6 Aug 01
CPMS Concurrence Signature / Date

Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development
5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

NDA #21-404 TEQUIN[®] (gatifloxacin HCl) Tablets
NDA #21-405 TEQUIN[®] (gatifloxacin HCl) for Injection

August 6, 2001

Mark J. Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV, HFD-590
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

**RE: USER FEE FORMS FOR JUNE 29, 2001 RESUBMISSION -
UNCOMPLICATED SKIN/SKIN STRUCTURE INFECTIONS**

Dear Dr. Goldberger:

Reference is made to NDA Numbers 21-404 and 21-405, TEQUIN[®] (gatifloxacin) Tablets and Injection and the conversation with Ms. Diana Willard of your Division on August 3, 2001.

Attached are the User Fee Forms 3397 for the June 29, 2001 resubmission (Uncomplicated Skin/Skin Structure Infections) in response to the Division's administrative needs. This resubmission, however, is not subjected to a user fee.

If you have any questions regarding this submission, please contact the undersigned at (203) 677-6370.

Sincerely,



Joan C. Fung-Tomc, Ph.D., ABMM
Director, Regulatory Science

/pk
Attachments



A Bristol-Myers Squibb Company

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Randall D. Curtiss Bristol-Myers Squibb Company P.O. Box 5400 Princeton, NJ 08543	3. PRODUCT NAME Tequin (gatifloxacin) Tablets
2. TELEPHONE NUMBER (Include Area Code) (609) 818-5220	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER N/A	6. LICENSE NUMBER / NDA NUMBER N021404

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

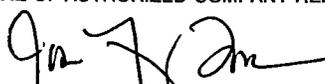
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director Regulatory Science	DATE June 29, 2001
---	---	------------------------------

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) User Fee Form for 6/29/01 Submission

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Joan C. Fung-Tomc, Ph.D., Director, Regulatory Science	DATE August 6, 2001
ADDRESS (Street, City, State, and ZIP Code) 5 Research Parkway, Wallingford, CT 06492		Telephone Number (203) 677-6370

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Dr., Room 3046 Rockville, MD 20852	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.
--	--	--

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

APPLICANT'S NAME AND ADDRESS

Randall D. Curtiss
Bristol-Myers Squibb Company
P.O. Box 5400
Princeton, NJ 08543

3. PRODUCT NAME

Tequin (gatifloxacin) Injection

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? **NO**
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(609) 818-5220

5. USER FEE I.D. NUMBER

N/A

6. LICENSE NUMBER / NDA NUMBER

N021405

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
- THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
- THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)
- A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
- THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

FOR BIOLOGICAL PRODUCTS ONLY

- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
- A CRUDE ALLERGENIC EXTRACT PRODUCT
- AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Director
Regulatory Science

DATE

June 29, 2001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Bristol-Myers Squibb Company	DATE OF SUBMISSION August 6, 2001
TELEPHONE NO. (Include Area Code) 203-677-6370	FACSIMILE (FAX) Number (Include Area Code) 203-677-7630
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 5 Research Parkway Wallingford, CT 06492	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously Issued)	21-405	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Gatifloxacin	PROPRIETARY NAME (trade name) IF ANY TEQUIN	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (±)-1-cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7- (3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate	CODE NAME (If any) BMS-206584	
DOSAGE FORM: I.V.	STRENGTHS: 200 mg & 400 mg	ROUTE OF ADMINISTRATION: Intravenous
(PROPOSED) INDICATION(S) FOR USE: Uncomplicated Skin/skin Structure Infections		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION User Fee Form for 6/29/01 Submission.
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA No. 21-061, IND Nos. 52-081, 53,521 and DMF No. (Pending)

This application contains the following items: (Check all that apply)

1. Index
2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))
4. Chemistry section
A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
15. Establishment description (21 CFR Part 600; if applicable)
16. Debarment certification (FD&C Act 306 (k)(1))
17. Field copy certification (21 CFR 314.50 (k)(3))
18. User Fee Cover Sheet (Form FDA 3397)
19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/> 20. OTHER (Specify) User Fee Form for 6/29/01 Submission

CERTIFICATION

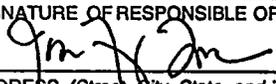
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Joan C. Fung-Tomc, Ph.D., Director, Regulatory Science	DATE August 6, 2001
ADDRESS (Street, City, State, and ZIP Code) 5 Research Parkway, Wallingford, CT 06492	Telephone Number (203) 677-6370	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH		OPDRA POSTMARKETING SAFETY REVIEW	
TO: Renata Albrecht, M.D., Acting Director Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590		FROM: Sarah J. Singer, R.Ph., Safety Evaluator Division of Drug Risk Evaluation II (DDRE II), HFD-440	OPDRA PID#, DATE: D010577 December 10, 2001
DATE REQUESTED: November 15, 2001	REQUESTOR: Ekopimo O. Ibia, M.D.		
DRUG: Gatifloxacin (Tequin®)	NDA #: 21-061, 21-062	SPONSOR: Bristol-Myers Squibb	
EVENTS: Update of earlier information on: <ol style="list-style-type: none"> 1. Abnormalities of glucose homeostasis 2. Torsade de pointes 			
EXECUTIVE SUMMARY: Because of Agency concerns that recent changes in the Tequin® labeling regarding glucose abnormalities still do not adequately convey the magnitude of gatifloxacin effects on glucose, OPDRA was asked to update the numbers of such events previously provided in August 2001. DSPIDP is currently considering a new indication for Tequin® and can use the opportunity to request additional labeling changes. OPDRA was also asked to update information on cases of gatifloxacin-associated torsade de pointes provided in August 2001. OPDRA suggested updating the numbers of those events for moxifloxacin and levofloxacin as well, to put the gatifloxacin numbers into perspective. Compared with the data provided in August 2001, the reporting rates rose slightly for serious U.S. gatifloxacin cases of both hypoglycemia and hyperglycemia, whereas the rates for levofloxacin stayed the same and the rate for moxifloxacin-associated hyperglycemia decreased (there are no AERS reports of serious U.S. cases of hypoglycemia associated with moxifloxacin). N.B.: Given the imprecision of both the numerators and denominators used to create the reporting rates, no conclusions should be drawn from these reporting rate changes. Comparing the "profound hyperglycemic events" reported with the three drugs, only gatifloxacin had higher counts of events than in August 2001. Regarding torsade de pointes, the specific gatifloxacin cases have changed somewhat from the earlier document because of slightly different inclusion criteria and followup information received; however, the number of cases remains the same and the case characteristics have not changed. The moxifloxacin cases are the same as those presented earlier. Levofloxacin torsade cases were not reviewed in the earlier document.			
REASON FOR REQUEST/REVIEW: In a document dated 8/13/01, OPDRA summarized AERS information on unlabeled adverse events reported with the most recently approved fluoroquinolones, gatifloxacin and moxifloxacin. Suggestions were made for changes to the product labeling for both drugs, including a recommendation that torsade de pointes and hyperosmolar hyperglycemic nonketosis be added to the Tequin® labeling. Bristol-Myers Squibb has agreed to add those events and in addition has worked with DSPIDP on other changes in the Tequin® labeling regarding glucose abnormalities. However, there is still concern within the Agency that the magnitude of the glucose abnormalities seen with gatifloxacin compared to other fluoroquinolones is not adequately addressed. Since a new indication for Tequin® is under consideration with an action date of 12/21/01, DSPIDP requested an update of the earlier numbers reported for the two events, to see if the picture has changed since the earlier document was written. OPDRA suggested updating the numbers for moxifloxacin and a somewhat older fluoroquinolone (levofloxacin) as well, to put the gatifloxacin numbers into perspective.			
RELEVANT PRODUCT LABELING: The wording of the Tequin® labeling has been somewhat strengthened in numerous sections that refer to glucose homeostasis. However, the phrase "as with other quinolones" is incorporated throughout, because glucose abnormalities are indeed reported to a certain degree with almost all fluoroquinolones. The concern in the Agency, however, is that the glucose abnormalities reported with gatifloxacin appear far more serious and higher in number than with the other drugs of the class, and it may not be appropriate to equate gatifloxacin to the other drugs. DSPIDP has therefore asked Bristol-Myers Squibb to strengthen its labeling even more.			

USAGE INFORMATION:

****Information from IMS HEALTH, INC. is copyrighted and cannot be used outside the FDA without prior clearance from IMS HEALTH.****

The following information from IMS HEALTH, INC. shows U.S. outpatient oral prescriptions and sales of drug to U.S. inpatient facilities from the date of approval of each drug through September 2001 and August 2001, respectively.

DRUG	APPROVAL DATE	National Prescription Audit Plus™: Oral prescriptions dispensed by U.S. retail pharmacies		Provider Perspective Audit™: Sales to U.S. inpatient facilities		
		Dates of data	Rx	Dates of data	MLs of IV	Tablets
Gatifloxacin	12/99	1/00 through 9/01	>	1/00 through 8/01		
Moxifloxacin	12/99	1/00 through 9/01	>	1/00 through 8/01		>
Levofloxacin	12/96	1/97 through 9/01	>	1/97 through 8/01		>

SEARCH DATES:

November 27 and 28, 2001

DATABASE SEARCHED:

Adverse Event Reporting System (AERS)

SEARCH CRITERIA:

Drug Names: Gatifloxacin (Tequin®)
Moxifloxacin (Avelox®)
Levofloxacin (Levaquin®)

MedDRA Terms:

1. Glucose abnormalities: Search criteria are described in the attachment (ATTACHMENT #1).
2. Torsade de pointe: Only that term was used.

SEARCH RESULTS:

See ATTACHMENT #1 and #2. The footnotes for each section of ATTACHMENT #1 indicate whether or not the cases were retrieved for hands-on analysis, allowing the merging of duplicate reports to yield only unique cases. In ATTACHMENT #2, all cases were retrieved and the table summarizes unique cases.

SUMMARY:

Compared with the data provided in August 2001, the reporting rates rose slightly for serious U.S. gatifloxacin cases of both hypoglycemia and hyperglycemia, whereas the rates for levofloxacin stayed the same and the rate for moxifloxacin-associated hyperglycemia decreased (there are no AERS reports of serious U.S. cases of hypoglycemia associated with moxifloxacin). **N.B.:** Given the imprecision of both the numerators and denominators used to create the reporting rates, no conclusions should be drawn from these reporting rate changes.

Comparing the "profound hyperglycemic events" reported with the three drugs, only gatifloxacin had higher counts of events than in August 2001.

Regarding torsade de pointes, the data is presented in a different format in this document than it had been in the August 2001 document. The specific gatifloxacin cases have changed somewhat from the earlier document because of slightly different inclusion criteria and followup information received; however, the number of cases remains the same and the case characteristics have not changed. The moxifloxacin cases are the same as those presented earlier. Levofloxacin torsade cases were not reviewed in the earlier document.

REVIEWER'S SIGNATURE / DATE:

/S/ 12/6/01

Sarah J. Singer, R.Ph.

TEAM LEADER'S SIGNATURE / DATE:

/S/ 12/6/01

Debra E. Boxwell, Pharm.D.

ACTING DIVISION DIRECTOR SIGNATURE / DATE:

/S/ 12/10/01

Julie Beitz, M.D.

ATTACHMENTS:

1. Glucose abnormalities reported with gatifloxacin, moxifloxacin, and levofloxacin
2. Torsade de pointes reported with gatifloxacin, moxifloxacin, and levofloxacin

Cc: NDA 21-061 / 21-062

HFD-590 Division File / Albrecht / Cavaille-Coll / Ibia / Willard

HFD-440 Beitz / Boxwell / Singer / Chron / Drug

Electronic File Name: c:\wfiles\gatiupdate.doc

ATTACHMENT #1
GLUCOSE ABNORMALITIES REPORTED WITH
GATIFLOXACIN, MOXIFLOXACIN, AND LEVOFLOXACIN

A. AERS CASES of GLUCOSE ABNORMALITIES with GATIFLOXACIN, MOXIFLOXACIN, or LEVOFLOXACIN as a SUSPECT DRUG (Searches performed 11/28/01)

HYPOGLYCEMIA

DRUG	ALL AERS CASES OF HYPOGLYCEMIA ^{1,2}	U.S. CASES OF SERIOUS ³ HYPOGLYCEMIA	U.S. ORAL OUTPATIENT Rx through 9/01 ⁴	U.S. SERIOUS HYPOGLYCEMIA REPORTING RATE outpatient Rx
Gatifloxacin	77	40	>	
Moxifloxacin	10	0	• >	
Levofloxacin	26	14	>	

HYPERGLYCEMIA

DRUG	ALL AERS CASES OF HYPERGLYCEMIA ^{5,6}	U.S. CASES OF SERIOUS ⁷ HYPERGLYCEMIA	U.S. ORAL OUTPATIENT Rx through 9/01 ⁸	U.S. SERIOUS HYPERGLYCEMIA REPORTING RATE outpatient Rx
Gatifloxacin	59	23	>	
Moxifloxacin	9	4	>	
Levofloxacin	19	8	>	

¹ AERS was searched for all cases coded either HYPOGLYCAEMIA NOS or BLOOD GLUCOSE DECREASED. The numbers are raw counts and probably include duplicates; in addition, there has been no attempt to evaluate the cases.

² Bristol-Myers Squibb has a waiver allowing nonreporting of nonserious labeled events for gatifloxacin; neither of the two other sponsors have such waivers for moxifloxacin or levofloxacin, so the gatifloxacin numbers are underreported in relation to the two other drugs.

³ Involving death, hospitalization, or disability, or considered life-threatening by the reporter. Negates differences caused by Bristol-Myers Squibb's waiver (see footnote 2).

⁴ Data obtained from the IMS HEALTH, INC. National Prescription Audit Plus™ database; information is copyrighted and cannot be used outside the FDA without prior permission from IMS HEALTH, INC.

⁵ AERS was searched for all cases coded either HYPERGLYCAEMIA NOS or BLOOD GLUCOSE INCREASED. The numbers are raw counts and probably include duplicates; in addition, there has been no attempt to evaluate the cases.

⁶ Bristol-Myers Squibb has a waiver allowing nonreporting of nonserious labeled events for gatifloxacin; neither of the two other sponsors have such waivers for moxifloxacin or levofloxacin, so the gatifloxacin numbers are underreported in relation to the two other drugs.

⁷ Involving death, hospitalization, or disability, or considered life-threatening by the reporter. Negates differences caused by Bristol-Myers Squibb's waiver (see footnote 6).

⁸ Data obtained from the IMS HEALTH, INC. National Prescription Audit Plus™ database; information is copyrighted and cannot be used outside the FDA without prior permission from IMS HEALTH, INC.

B. NEW-ONSET DIABETES and PROFOUND HYPERGLYCEMIC EVENTS REPORTED with GATIFLOXACIN, MOXIFLOXACIN, and LEVOFLOXACIN⁹

DRUG	EVENT	UNDUPLICATED CASES IN AERS
Gatifloxacin	Nonketotic hyperglycaemic-hyperosmolar coma	3*
	Diabetic hyperosmolar non ketoacidosis	1
	New-onset diabetes	6*
	Diabetic ketoacidosis	1
Moxifloxacin	—	0
Levofloxacin	Diabetic ketoacidosis	1
	New-onset diabetes	2

*One case was coded with both terms; there were 10 total cases for gatifloxacin.

⁹ AERS was searched on 11/27/01 for cases coded with any of the following terms: DIABETES MELLITUS NOS, DIABETIC COMA NOS, DIABETIC HYPEROSMOLAR NON KETOACIDOSIS, DIABETIC KETOACIDOSIS, or NONKETOTIC HYPERGLYCAEMIC-HYPEROSMOLAR COMA. All cases were obtained for hands-on review so the numbers above represent unique cases.

**ATTACHMENT #2
TORSADE DE POINTES CASES REPORTED WITH
GATIFLOXACIN, MOXIFLOXACIN AND LEVOFLOXACIN**

A. GATIFLOXACIN TORSADE CASES IN AERS as of 11/28/01							
CASE #	AGE	TIME TO ONSET (days)	HISTORY	ELECTROLYTES	CONCOMITANT MEDS	POSITIVE DECHALLENGE?	EVENT
1 3474727 10379618 Hosp OK	83 Male 176 lb	1 (3 for fluconazole) 400 mg IV, then 200 mg QD PO Infection	Intestinal obstruction	K 4.1 Mg 1.9 Ca 8.9	Fluconazole (also suspect), atenolol, enoxaparin, ranitidine, hydrocodone / acetaminophen	Yes	The patient developed infection following surgery for an obstructive colon. His EKG showed a QT of 340-360 msec. He was given a loading dose of IV gatifloxacin 400 mg, then started on 200 mg PO the following day. Later that day he went into torsade; his EKG at that time showed a QT of 416 msec. Gatifloxacin was discontinued and the following day his QT was back to baseline. The patient's BUN and creatinine were slightly elevated (66 and 2.3).
2 3582305 10631182 CA	47 Female	<1 400 mg IV Fever	Severe congenital heart block, pacemaker	K 2.4	Fluconazole		Patient developed a clot on her pacemaker wire so an "artificial heart" was implanted. Gatifloxacin was given after the procedure and the patient subsequently experienced several runs of torsade de pointes which continued for several days.
3 3589596 Direct Death IN	85 Female	<1 400 mg IV Fever	Severe aortic stenosis, congestive heart failure		Amiodarone (also suspect), furosemide, nitroglycerin, promethazine, lorazepam, KCl, acetylsalicylic acid		Patient was given one dose of gatifloxacin in ER for high fever and transported to cardiac ICU for management of congestive heart failure. She was started on an infusion of amiodarone for tachycardia. Shortly after the infusion was started, she developed torsade de pointes and expired despite significant resuscitation efforts over 90 minutes.
4 3598342 1067-396 Life-threatening ME	81 Female	3 400 mg PO QD Respiratory infection	Atrial fibrillation, mild congestive heart failure, chronic blood loss, chronic renal insufficiency, anemia, diabetes		Amiodarone, isosorbide mononitrate, omeprazole, bumetanide, potassium, glyburide	Yes	The patient had developed Staph aureus bacteremia secondary to a line site infection and was given ceftriaxone while in the hospital. On discharge she was given a prescription for levofloxacin. Three days later she was readmitted after two syncope episodes. Diagnosis: ventricular tachycardia and torsade de pointes. Gatifloxacin was discontinued and she recovered.
5 3613919 10716777 Life-threatening CT	66 Female 134 lb	<1 400 mg PO URI	Coronary artery disease with PTCA and RCA stent	Na 142 K 4.0 Mg 2.1 Ca++ 8.8	Amitriptyline, pravastatin, omeprazole, rofecoxib, hydrocodone/acetaminophen, valsartan	Yes	Patient developed prolonged QTc (>500 msec) and syncope two hours after first dose of gatifloxacin. Found to be in third-degree heart block with runs of torsade de pointes.

A. GATIFLOXACIN TORSADE CASES IN AERS as of 11/12/8101

CASE # AERS # MFR # OUTCOME ORIGIN	AGE SEX WEIGHT	TIME TO ONSET (days) DOSE, ROUTE INDICA- TION	HISTORY	ELECTRO- LYTES	CONCOMITANT MEDS	POSITIVE DECHAL- LENGER?	EVENT
6 3622127 Direct Life- threatening IL	78 Female 196 lb	2 400 mg Pneumonia			Atorvastatin, hydrochloro- thiazide, amlodipine, metformin, diclofenac		Patient was hospitalized two days after starting gatifloxacin and torsade was diagnosed. The drug was discontinued. The physician was contacted for additional information and stated that the patient had no history of arrhythmia or predisposing condition such as electrolyte abnormalities, and alternate explanations had been ruled out.
7 3705729 10968196 Death CT	74 Male	3 400 mg QD IV/ Pneumonia	Coronary artery disease and senile amyloidosis found on autopsy	K 3.1 Mg 1.9	Metoprolol, omeprazole, enalapril, furosemide, vancomycin		Patient's pretreatment QTc was 443 msec. After first dose of gatifloxacin, it increased to 512. Less than two hours after his third dose, he developed torsade de pointes and cardiopulmonary arrest. He failed to regain cerebral function and life support was discontinued the next day.
8 3685041 Direct Life- threatening IL	85 Female 85 lb	<1 400 mg IV Pneumonia	End-stage Parkinson's disease	K 3.5 prior to event, Mg 1.8 three hours after event (Mg had been given)	Paroxetine, carbidopa/ levodopa, pergolide mesylate	Yes	ER patient was noted to have four runs of nonsustained ventricular tachycardia less than two hours after the first dose of gatifloxacin. Amiodarone was started and the patient was transferred to the cardiac ICU. There the original runs were identified as having been torsades. Amiodarone was DC'd and magnesium was started. No further gatifloxacin was given and no further torsade occurred.
9 3722816 11017084 Hosp Canada	70 Male	2 400 mg QD PO Bronchitis	Cardiac insufficiency, diabetes mellitus		Simvastatin, furosemide, tamsulosin, flurazepam, clopidogrel, ASA	Yes	The patient had two syncope episodes following his second dose of gatifloxacin, and was hospitalized with a diagnosis of torsade.
3496928 10403103 Hosp CT	79 Female	1 400 mg QD PO ?UTI	Severe congestive heart failure, bradycardia, syncope, implanted defibrillator / pacemaker	K 3.4 Mg 1.7 Na 126	Sotalol (also suspect), nifedipine, lorazepam, simvastatin, warfarin, aspirin	Yes	The patient had been on sotalol with a QTc=428 msec. After one dose of gatifloxacin, QTc=540 msec. The patient developed three episodes of ventricular tachycardia, later stated to be torsade, but called only ventricular tachycardia in a published article. Gatifloxacin was discontinued while sotalol was continued; the QTc returned to 420 msec.

The following case was included in the safety review document of 8/13/01, but when Dr. Douglas Shaffer of OPDRA later reviewed the physician-supplied ECGs for the case, he found no evidence of torsade de pointes. Subsequent review of the published article showed that the event was not categorized as torsade in the publication either, although it had been reported to Bristol-Myers Squibb as a case of torsade.

B. MOXIFLOXACIN TORSADE CASES IN AERS as of 11/28/01

CASE # AERS # MFR # OUTCOME ORIGIN	AGE SEX WEIGHT	TIME TO ONSET (days) DOSE INDICA- TION	HISTORY	ELECTRO- LYTES	CONCOMITANT MEDS	POSITIVE DECHAL- LENGE?	EVENT
1 3445074 1200002333 Life- threatening Germany	83 Female	3 400 mg QD Broncho- pneumonia	Coronary disease, sick sinus syndrome, pacemaker, cardiac insufficiency, stroke, renal failure	K 2.98 the day before; KCl was infused	Digloxin, captopril, furosemide, isosorbide dinitrate, theophylline, acetylcysteine, hydrochloro- thiazide, enoxaparin, mepiprone (a butyropheneone tranquillizer)		The patient had been hospitalized for bronchopneumonia with decompensated right and left heart failure. Two days later she had improved and was transferred to a normal ward. The next day IV cefuroxime was switched to moxifloxacin. The following day hypokalemia was discovered and treated with IV KCl. That night she was found on the toilet with signs of convulsions and apparent cardiorespiratory arrest. CPR was given and she was retransferred to the ICU. ECG showed QT=490 msec with a mild U wave. The next day when she received her moxifloxacin an ECG showed QT=510 msec; no K was measured. Four hours later torsade occurred. She received cardioversion, moxifloxacin was discontinued, and amiodarone and Mg were started. The following day QT prolongation occurred and the patient went into a coma; amiodarone and magnesium were discontinued. The patient had a prolonged course in the ICU but no further ventricular arrhythmia was documented
2 3613365 200110514 GDS Life- threatening Switzerland	78 Female	4 400 mg QD PO Acute bronchitis	Atrial flutter, tachycardia, ventricular extrasystoles, aortic valve replacement, nephrectomy for renal tuberculosis, slight renal impairment		Amiodarone (also suspect), metoprolol, furosemide, aspirin		Three days after starting moxifloxacin, patient felt unwell and complained of dyspnea. Later that day she lost consciousness. An ECG at the physician's office revealed bradycardic atrial fibrillation, bigeminy, and QT prolongation. She was hospitalized and later that day developed ventricular tachycardia "with TQP like shape". Cardiac massage was performed and magnesium and lidocaine were infused. Amiodarone and metoprolol were discontinued but moxifloxacin was continued. The following day the patient had sinus bradycardia with a QTc of 497 msec. The next day she had tachycardia with a QTc of 483. She was transferred to another hospital where moxifloxacin was discontinued because of its QT-prolonging effects. However, she continued to have prolonged QT measurements (up to 700) and eventually a pacemaker was implanted for "symptomatic sinus bradycardia due to sick sinus syndrome".
3 3626034 200113883 GDS Life- threatening Austria	84 Female	1 400 mg PO QD Pneumonia	Atrial fibrillation, left ventricular failure, diverticulosis		Digloxin, molsidomine, hydrochloro- thiazide, clopidogrel		Hospitalized patient had an admission QT of 480 msec. Five days later moxifloxacin was started for nosocomial pneumonia. The following day she experienced acute circulatory arrest. Heart massage was started and the patient responded without the use of any drugs. She was transferred to the ICU where a monitor showed runs of ventricular tachycardia, some of which "were of TQP shape". At one point she experienced loss of consciousness. Magnesium was started and moxifloxacin, digloxin, and hydrochlorothiazide were discontinued. During workup the patient was diagnosed with "bradycardia-tachycardia syndrome" and a pacemaker was implanted two weeks later. However, approximately one week after that the patient developed syncope and fell. An ECG showed atrial fibrillation and extrasystoles. She died the day after the fall despite resuscitation attempts.

C. LEVOFLOXACIN TORSADE CASES IN AERS as of 11/28/01

CASE # AERS # MFR # OUTCOME ORIGIN	AGE SEX WEIGHT	TIME TO ONSET (days) DOSE, ROUTE INDICA- TION	HISTORY	ELECTRO- LYTES	CONCOMITANT MEDS	POSITIVE DECHAL- LENGE?	EVENT
1 3017664 980213- 107050899 Life- threatening NY	73 Female	6 500 mg QD PO UTI	Coronary disease, hypertension, dilated cardio- myopathy, old non-Q wave myocardial infarct, diabetes		Atenolol, lisinopril, furosemide, aspirin (all long- term with no recent adjustment in dosage)		The patient was hospitalized with a urinary tract infection and levofloxacin was started. Three days later she had shortness of breath, an EKG showed a new Q wave but cardiac enzymes were within normal limits so she was thought to be having an exacerbation of congestive heart failure (which is not listed under History on the report). She was transferred to the CCU and given "extra" furosemide. The next day during heart catheterization she was found to have a prolonged QT and she developed torsade while the dye was being injected.
2 3407811 980108- 107050098 Medically significant PA	88 Female	4 500 mg QD IV Bronchitis	Atrial fibrillation, congestive heart failure, ischemic heart disease, bronchitis	WNL	Procainamide, albuterol, corticosteroids, furosemide	Yes	The patient was hospitalized for atrial fibrillation, mild congestive heart failure, and bronchitis. Her QTc=450 msec. She was started on levofloxacin, albuterol, steroids, and furosemide. She also received one dose of procainamide 500 mg but it was discontinued when records showed the atrial fibrillation was intermittent. Three days later her QTc=464 msec; the procainamide level was 1.8 µg/ml (therapeutic range 4.0-10.0). The next day QTc=568 msec and the patient developed torsade; later that day QTc=577 msec. Levofloxacin was discontinued with no other medication changes. The next day QTc=469, the following day QTc=437 msec and the patient had no further episodes of torsade. The case was later published: Samaha FF. QTc interval prolongation and polymorphic ventricular tachycardia in association with levofloxacin [letter]. Am J Med 1999;107:528-9.
3 3036721 Direct Life- threatening NY	81 Female	8 500 mg QD IV Aspiration pneumonia	Parkinson disease		Donepezil, L-thyroxine, levodopa/ carbidopa, omeprazole	Yes with supportive treatment.	A patient with a hip fracture developed aspiration pneumonia and levofloxacin was started. Creatinine ranged from 0.86-1.16 mg/dl. Eight days later, the patient experienced torsade and levofloxacin was discontinued. The torsade resolved spontaneously and required only supportive treatment/monitoring
4 3184901 981221- 057015107 Life- threatening Japan	59 Male	9 500 mg QD IV Pneumonia	Atrial fibrillation, hypertension, ischemic cardio- myopathy, heart failure, respiratory insufficiency from pulmonary edema		Captopril, digoxin, levomepro- mazine, dipyron		The patient was hospitalized with pulmonary edema. He had a marked cardiovascular risk profile and "metabolic syndrome". Recurrent pulmonary infiltration developed. He was treated with high-dose diuretics and ACE inhibitors. Nine days after starting levofloxacin, he had two episodes of ventricular tachycardia, one of which was torsade.

C. LEVOFLOXACIN TORSADE CASES IN AERS as of 11/28/01

CASE #	AGE	TIME TO ONSET (days)	HISTORY	ELECTROLYTES	CONCOMITANT MEDS	POSITIVE DECHALLENGE?	EVENT
5 AERS # 3230116 MFR # 990303-107051709 OUTCOME Hosp ORIGIN WI	87 Male	PO (no dose listed) Not stated		Hypokalemia	Digoxin, captopril, hydrochlorothiazide		After starting levofloxacin, the patient was hospitalized for syncope. EKG showed torsade. He was found to be hypokalemic.
6 AERS # 3272112 MFR # 990326-107011227 OUTCOME Life-threatening ORIGIN NJ	46 Female 140 lb	1 500 mg QD PO URI	Syncope, hypothyroidism, mixed connective tissue disorder	Ca low but appropriate for level of albumin	l-thyroxine, prednisone	No	The patient was hospitalized after developing syncope. EKG showed QT=>600 msec and torsade. Levofloxacin was discontinued but QT prolongation of >500 msec and torsade persisted more than one week. An echocardiogram was normal. Patient had a cardioverter/defibrillator implanted because of her risk of sudden cardiac death.
7 AERS # 3256499 MFR # PRJUSA1999000938 OUTCOME Medically significant ORIGIN MN	77 Female	1 PO (no dose listed) Not stated	Atrial fibrillation, cardiac myopathy	K, Na, Cl WNL	Sotalolol, captopril, diltiazem, furosemide, KCl		The patient received her first dose of levofloxacin and her QT increased from 480 msec to 630 msec. After her second dose, her QT increased to 688 msec, followed three hours later by torsade which was successfully treated.
8 AERS # 3242441 MFR # 990329-107011252 OUTCOME Hosp ORIGIN TX	82 Male	2 500 mg QD IV Pneumonia	Atrial fibrillation, right bundle-branch block, hypertension, bipolar disorder, Alzheimer's disease	Lithium, digoxin		Yes	The patient was hospitalized with fever, nausea / vomiting, cough, and decreased responsiveness. Two days after starting levofloxacin for pneumonia, he went into cardiac arrest and an EKG showed torsade. He was resuscitated, levofloxacin was discontinued, and he had no further episodes. The cardiologist originally thought the arrhythmia might be due to lithium, but its level was 0.3.
9 AERS # 3423154 MFR # PRJUSA2000000317 OUTCOME Medically significant ORIGIN IL					Propylthiouracil, digoxin, atenolol		The patient developed torsade while on levofloxacin. All other information except concomitant medications is unknown.
10 AERS # 3440245 MFR # A005485 OUTCOME Required Intervention ORIGIN PA	82 Male 135 lb	31 (3 for fluconazole) 500 mg QD IV Pneumonia	Left bundle-branch block		Fluconazole (also suspect)		The patient was hospitalized for respiratory failure and started on levofloxacin. Fluconazole was started for a fungal urinary tract infection 28 days later, three days after that the patient demonstrated ventricular tachycardia with a prolonged QT. Torsade was suspected but not proven since the patient was not on 12-lead telemetry. Both suspect drugs were discontinued.

C. LEVOFLOXACIN TORSADE CASES IN AERS as of 11/28/01

CASE #	AGE	TIME TO ONSET (days)	HISTORY	ELECTROLYTES	CONCOMITANT MEDS	POSITIVE DECHALLENGER?	EVENT
11 3450489 Direct Life-threatening CT	64 Male	1 PO then IV Prostatitis	Coronary disease, a myocardial infarct one month earlier, prostatic hypertrophy, sleep apnea	K, Mg WNL	Amiodarone		In the evening of the day he took his first dose of levofloxacin, the patient was seen in the ER with lightheadedness and cardiac complaints. He was cardioverted several times and admitted; PO levofloxacin was switched to IV. The report says "he had also been started on amiodarone that day" but doesn't say if that was before or after the cardiac events were first reported. His QTc one month prior had been 408 msec; in the ER it was 480. Two days later he developed torsades then ventricular fibrillation; QTc=500 msec. He later coded and was resuscitated and restarted on an amiodarone drip. The next day he underwent angioplasty and internal defibrillator placement.
12 3504694 Direct Death CT	69 Female 170 lb	2 500 mg QD AECB	Atrial fibrillation, congestive heart failure, sinus bradycardia	K 2.9 Ca 1.21 mmol/l Mg 1.8	Amiodarone (also suspect), omeprazole, metronidazole		The patient had chronic congestive heart failure, atrial fibrillation, and sinus bradycardia and was stable on amiodarone with a QTc=438 msec. One day after levofloxacin was started her QT increased and she developed torsade. It deteriorated to ventricular fibrillation and she could not be resuscitated.
13 3628545 Direct Death PA	Male	<1 Bronchitis	Cardiomyopathy, AICD				Patient developed torsade four hours after taking levofloxacin. No other information given.
14 3635319 NSADSS 2001007195 Death MI		8 IV	Heart transplant				Patient was given 2 doses of IV levofloxacin. Eight days later developed torsade and expired. Not thought to have any relationship to levofloxacin. No other information provided.
15 3644749 Direct Required intervention MS	67 Female 129 lb	1 500 mg IV QD Possible pneumonitis/sepsis	Recent atrial fibrillation, prolonged QT, type 2 diabetes, mental retardation, gallbladder disease, thrombocytopenia	Hypo-kalemia, hypomagnesemia	Sotalol (also suspect)		Patient was admitted with atrial fibrillation and a prolonged QT. Next day was started on sotalol. The following day levofloxacin was started. The day after that she developed torsade and was found to be hypomagnesemic and hypokalemic. Sotalol was discontinued but levofloxacin was continued for 8 more days.

C. LEVOFLOXACIN TORSADE CASES IN AERS as of 11/28/01

CASE #	AGE	TIME TO ONSET (days)	HISTORY	ELECTRO-LYTES	CONCOMITANT MEDS	POSITIVE DECHARGE-LENGER?	EVENT
16 3652409 NSADSS 2001012165 Hosp France	72 Male	1 500 mg BID PO Pneumonia	Atrial fibrillation/ flutter, hypertension, obesity, aortic aneurysm, chronic bronchitis	Hypo- kalemia	Amiodarone, nicardipine, furosemide (all of the above also considered suspect), losartan, aspirin	Yes	One day after starting levofloxacin, patient was hospitalized for hypokalemia, QT prolongation (>600) and torsade. Levofloxacin, amiodarone, and furosemide were discontinued and potassium was administered, first IV then orally.
17 3653549 Direct Life- threatening MO	78 Male 164 lb	1 500 mg IV QD Pneumonia	Acute MI with atrial fibrillation, severe renal failure on dialysis	K, Mg WNL	Amiodarone (also suspect)	Yes	Patient had experienced an MI with atrial fibrillation. Was placed on amiodarone. Two days later was started on levofloxacin. He had QTc prolongation at 440 msec, then developed torsade de pointes and cardiac arrest—pulseless ventricular fibrillation. He was shocked twice and recovered. He arrested during dialysis.
18 3667625 NSADSS 2001016957 Hosp Canada	44 Female 229 lb	7 250 mg PO QD Chest infection	No cardiac problems, hepatitis C, diabetes, asthma, psychiatric problems	Low Mg	Levo- meprobamate, theophylline, zopiclone, netazadone, citalopram, sabalumol, propranolol, quetiapine		Patient was prescribed levofloxacin for a chest infection. Over the next few days, she had several spells of syncope, the last of which was 4 days prior to admission. On admission, she was normotensive. Her theophylline levels were elevated (no levels given). Seven days after starting levofloxacin, a cardiology consult at rest found a prolonged QT interval, left axis deviation, near-left anterior hemiblock and nonspecific ST changes. Diagnosis: recurrent syncope possibly due to torsade. Telemetry showed QTc=499. Because the QT stayed prolonged, magnesium levels were ordered and were 0.64 eight days after admission (normal 0.66-0.95); patient was placed on oral magnesium.
19 3693151 Direct Hosp USA	73 Female 110 lb	1 500 mg PO QD Pneumonia			Dofetilide (also suspect), diltiazem, ethinyl estradiol, HCTZ, lanoprazole, warfarin, enoxaparin	Yes	Patient started dofetilide and levofloxacin the same day, for atrial fibrillation and pneumonia respectively. An ECG taken after the 3 rd dose of dofetilide (the next day) showed QT/QTc prolongation (496/610). Shortly thereafter the patient developed torsade, which resolved after the administration of IV magnesium. Dofetilide was stopped and the QT interval decreased but continued to fluctuate and increased to 630 the following day, after a dose of levofloxacin. Levofloxacin was stopped and the patient stabilized sufficiently to be discharged 5 days later. The possibility of an underlying prolonged QT syndrome was raised.
20 3706677 NSADSS 2001025157 Medically significant Austria	70 Female	500 mg IV QD UTI	*Enzymatic infarction, broncho- pneumonia, cholestasis, gastroenteritis urinary calculus		Enalapril, alprazolam, dipyron, metoclopramide, dalleparin		Patient received levofloxacin for 5 days. On an unspecified date she experienced tachycardia, extrasystole, and torsade de pointes. The events resolved completely on an unspecified date.

C. LEVOFLOXACIN TORSADE CASES IN AERS as of 11/28/01

CASE #	AGE	TIME TO ONSET (days)	HISTORY	ELECTROLYTES	CONCOMITANT MEDS	POSITIVE DECHAL. LENGTH?	EVENT
21 3724171 NSADSS 2001031556 Life-threatening MI	30 Female	250 mg PO q 48 h Pneumonia	Acute renal & hepatic failure, on hemodialysis		Fluconazole (also suspect), ranitidine, piperacillin / tazobactam	Yes	Patient had a run of ventricular fibrillation and was given DC cardioversion twice with a return to normal sinus rhythm. Was transferred to the ICU and had recurrent ventricular fibrillation with return to normal sinus rhythm after one cardioversion. The strip revealed prolonged QT and torsade de pointes.
22 3729626 Direct Life-threatening CA	47 Male	1 500 mg PO QD			Azithromycin (also suspect)	Yes	Patient had been given one 1-gram dose of azithromycin for an unspecified indication. Eight days later he was started on levofloxacin and developed a prolonged QT interval and "torsade-like arrhythmia" on the second day.

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

/s/

Sarah Singer
12/10/01 02:58:39 PM
PHARMACIST

Julie Beitz
12/10/01 04:51:27 PM
DIRECTOR

NDA 21-404
NDA 21-405
NDA 21-061/S-010
NDA 21-062/S-011
NDA 21-061/S-016
NDA 21-062/S-017

Acting Division Director's Memo to the File

Date: July 30, 2002

Sponsor: Bristol Myers Squibb (BMS)

Applications: NDA 21-061 (Tequin® Tablets)
NDA 21-061 (Tequin® Injection)

Purpose of memo

The purpose of this memorandum is to provide a summary of the gatifloxacin regulatory review and action history for the indication of uncomplicated skin and skin structure infections. This memo also provides a summary of the safety issues regarding the effect of gatifloxacin on the QT interval (prolongation) and glucose homeostasis (including symptomatic hypoglycemia and/or hyperglycemia).

Background

NDAs 21-061 and 21-062, submitted by BMS on December 28, 1998, requested approval for use of Tequin® in the treatment of community-acquired pneumonia, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis (AECB), uncomplicated urinary tract infections, complicated urinary tract infections and pyelonephritis, uncomplicated gonorrhea, and uncomplicated skin and skin structure infections (USSSI). These two NDAs were approved on December 17, 1999 for all of the BMS proposed indications except uncomplicated skin and skin structure infections and marketed thereafter. Regarding the skin indication, the December 17, 1999 approval letter stated that "...we have concluded that the indication of uncomplicated skin and skin structure infections is approvable pending submission of post-marketing data confirming the safety of gatifloxacin and therefore demonstrating an acceptable risk/benefit profile." The Agency believed that the database submitted in the original NDAs was too small to make a reliable risk/benefit assessment of the safety profile of gatifloxacin for this use. Five of the seven post-marketing agreements outlined in the December 17, 1999 approval letter were designed to address the safety concern noted above. These five agreements, which BMS concurred with in their December 16, 1999 letter to the Division, are as follows:

- a safety study of at least 15,000 patients,
- an evaluation of spontaneously-reported post-marketing adverse event reports (ADR) for at least one million patient exposures worldwide,
- and three pharmacokinetic studies evaluating the effect of gatifloxacin on the QT interval.

Information from the five post-marketing agreements outlined above was submitted by BMS as correspondence to IND 52,081 on February 7, 2001. After reviewing the contents of this February 7, 2001 submission, the Division contacted BMS on March 15, 2001 to advise the company that if their intent was for the FDA to review this information in support of approval of the skin indication, the information needed to be submitted to NDAs 21-061 and 21-062 as efficacy supplements. Efficacy supplements requesting approval for the use of Tequin in USSSI were submitted to NDAs 21-061 and 21-062 on June 29, 2001 (received on July 2, 2002). For the FDA's administrative purposes, these resubmissions to the December 17, 1999 approval letter for USSSI were designated as NDAs 21-404 (Tequin Tablets) and 21-405 (Tequin Injection). The 6 month User Fee Goal Dates for these administrative NDAs was January 2, 2002.

Although at the time of approval of NDAs 21-061 and 21-062 the Agency's main safety concern was the effect of gatifloxacin on QT prolongation, another safety signal regarding glucose homeostasis with Tequin administration was detected during post-marketing surveillance. Review of data in the June 29, 2001 resubmissions combined with safety information analyzed by FDA staff from post-marketing reports received through the MedWatch system (July 13, 2000, August 13, 2001, and December 10, 2001 reviews by Ms. Sally Singer of the Office of Post Marketing Drug Risk and Assessment {now the Office of Drug Safety}) led the Division to propose revised labeling to BMS that included information regarding gatifloxacin's effect on glucose homeostasis. This effect includes both symptomatic hyperglycemia and hypoglycemia. Disturbances of glucose homeostasis were reported predominantly in diabetic patients, a population at increased risk for skin and skin structure infections.

The Division proposed labeling revisions to BMS that included not only the new indication of USSSI but also updated information regarding gatifloxacin's effects on glucose homeostasis and QT prolongation. The revisions the Division proposed regarding glucose homeostasis were in the **CLINICAL PHARMACOLOGY: Glucose Homeostasis, WARNINGS, PRECAUTIONS: General, Information to Patients, Drug Interactions/Antidiabetic agents, and Geriatric Use,** and **ANIMAL PHARMACOLOGY** sections of the label. In addition, revisions were proposed to the labeling under **CLINICAL PHARMACOLOGY/Electrocardiogram** and **WARNINGS** regarding gatifloxacin's effect on QT prolongation. These proposed labeling revisions were discussed with BMS prior to the January 2, 2002 User Fee Goal Date for the June 29, 2001 resubmissions. An agreement between BMS and the Division, however, was not reached and a second approvable letter for the USSSI indication issued on December 21, 2001. This letter indicated that approval was contingent on acceptable labeling; no other conditions for approval of the USSSI indication were stated.

The Divisions' expectation was that a resubmission containing only proposed revised labeling would be BMS' response to the December 21, 2001 approvable letter and that labeling agreed upon by both BMS and the Division could be negotiated within a short timeframe. On February 6, 2002, BMS submitted proposed revised labeling in response to the December 21, 2001 approvable letter. Included in this February 6, 2002 submission was the final study report for Study CV123-229 entitled "Pravastatin or atorvastatin evaluation and infection therapy (PROVE IT): ECG substudy of gatifloxacin effects on the QTc interval." This study evaluated the effect of gatifloxacin on coronary artery disease and included information regarding gatifloxacin's QT effects. BMS was advised that separate labeling supplements containing only the data from the PROVE IT ECG substudy and proposed labeling revisions based on this study could be submitted. BMS elected to keep the USSSI resubmissions and the PROVE IT study data with its associated labeling revisions combined. The 6 month User Fee Goal Date for these resubmissions was August 7, 2002.

On April 4, 2002, BMS submitted proposed labeling revisions regarding glucose homeostasis based on an executive summary of Study AI420-105 entitled "Open-label Study of the Reversibility of the Effect of Gatifloxacin on Insulin Secretion Following Oral Glucose Challenge in Type 2 Diabetics" to NDAs 21-404 and 21-405. The Division, as had been explained to BMS prior to the April 4, 2002 submissions, considers an executive summary to be a preliminary report that would not be sufficient as the basis for labeling changes. BMS indicated that the final study report for Study A1420-105 would be available by late summer 2002.

The Division requested a teleconference with BMS to discuss the "seemingly rolling pattern of requesting changes to the package insert" while the review for the USSSI resubmissions was underway. This teleconference was held on April 16, 2002. As the December 17, 1999 approval letter had stated that the USSSI indication was "...approvable pending submission of data confirming the safety of gatifloxacin and therefore demonstrating an acceptable risk/benefit profile," an approval action for this indication could not issue until all the available safety data had been reviewed and labeling negotiated. These safety data would include the data from Studies CV123-229 and AI420-105. Dr. Albrecht explained that "... a regulatory problem occurs when related 'rolling' submissions are made that do not allow us to bring to closure any one issue." BMS and the Division agreed that the April 4, 2002 submission to NDAs 21-404 and 21-405 containing the executive summary for Study AI420-105 would be considered correspondences. BMS and the Division further agreed that BMS would send by facsimile transmission labeling regarding glucose homeostasis for the Division to review. After the Division had reviewed the proposed labeling and provided any comments to BMS, "Changes Being Effectuated" supplements (CBEs) would be submitted. NDAs 21-061/S-016 and 21-062/S-017 were submitted as CBE supplements on May 10, 2002. The Division stated during the April 16, 2002 teleconference that an action on these CBE supplements would occur at the same time that an action was taken on the February 6, 2002 USSSI resubmissions.

Relevant to the "rolling" submissions, reviews and labeling negotiations was information provided to FDA at the end of the April 16, 2002 teleconference. Dr. Nicaise from BMS informed the Division that the European authorities reviewing the Grunenthal (not BMS) gatifloxacin applications were considering a **CONTRAINDICATION** to the use of gatifloxacin in patients with diabetes mellitus due to the effect of gatifloxacin on glucose homeostasis. As the Division already had reservations about approving a skin indication without the totality of the safety information requested in the December 21, 2001 USSSI approvable letter, this information added a new level of concern. Dr. Albrecht stated that the Division would like further information, including the wording proposed for the label regarding glucose homeostasis, about the European decision.

On June 11, 2002, a teleconference between BMS and the Division was held to discuss the European review process and the possibility that the European authorities might contraindicate the use of gatifloxacin in patients with diabetes mellitus. Dr. Nicaise outlined the complex regulatory process in Europe during this teleconference. Dr. Albrecht stated that it would be helpful to the Division to receive in writing what information the European authorities employed in their decision-making process. She explained that if different policies and regulations exist between the two Agencies, it would be useful for the Division to have an explanation of the totality of these differences. The Division requested that BMS certify in writing that all the pre- and post-approval safety information available to the European authorities that led to their proposal of a **CONTRAINDICATION** to the use of gatifloxacin in patients with diabetes mellitus has been submitted to the Agency. If different conclusions were reached from the same

data, it may simply be due to different scientific interpretations of the same data and/or employment of different parameters in arriving at a conclusion.

The request for certification that all the pre-and post-approval safety information available to the European authorities had been submitted to the Agency was repeated during several subsequent telephone conversations between Dr. Joan Fung-Tomc from BMS and Ms. Diana Willard from the Division of Special Pathogen and Immunologic Drug Products. The July 29, 2002 submissions to INDs 52,081, 53,521, and 57,672 contained a copy of the documentation submitted to the European authorities but not the requested certification. The Division strongly believes that the indication of USSSI cannot be responsibly approved without certification that all the pre-and post-approval safety information available to the European authorities that led to their proposal of a **CONTRAINICATION** to the use of gatifloxacin in patients with diabetes mellitus has been submitted to the Agency.

A third approvable letter for the USSSI indication (administrative NDAs 21-404 and 21-405) issued on August 2, 2002. This letter included approvable actions for NDA 21-061/S-010 and NDA 21-062/S-011 (QT prolongation) and for NDA 21-061/S-016 and NDA 21-062/S-017 (glucose homeostasis). As conditions of approval, this letter stated that BMS must:

- Provide certification, as was discussed with and agreed to by Dr. Nicaise of Bristol-Myers Squibb during a teleconference with the Division on June 11, 2002, that all the safety information on Tequin submitted in Europe has previously been submitted to the Agency.
- Submit draft labeling identical in content to the enclosed labeling (text for the package insert). In addition, it will also be necessary for BMS to reference their July 29, 2002 submission that contained the artwork for the primary bag for the Tequin® Injection minibags.

An August 23, 2002 submission from BMS contained the certification requested by the Division in the August 2, 2002 approvable letter regarding the safety information for gatifloxacin filed in the European marketing application. The August 23, 2002 submission also contained proposed revised labeling to NDA 21-404, NDA 21-405, NDA 21-061/S-010 and S-016, and NDA 21-062/S-011 and S-017 in response to the August 2, 2002 approvable letter. The User Fee Goal Date for these resubmissions is February 26, 2003.

Relevant to the above summary of the gatifloxacin regulatory review and action history for the indication of uncomplicated skin and skin structure infections is the following:

- NDA 21-061/S-007 (Tequin Tablets) dated December 21, 2000 and NDA 21-062/S-008 (Tequin for Injection) dated January 2, 2001 provided for a change in the dosing regimen for the treatment of acute exacerbation of chronic bronchitis (AECB) to five days duration (the indication for AECB had originally been approved for 7 to 10 day duration on December 17, 1999). These efficacy supplements were approved on October 12, 2001.

These supplements are mentioned in this memo to explain why the Division believed they could be approved without incorporating the safety information required for approval for the USSSI indication. As the AECB indication was already approved, the Division believes that the change in dosing regimen (reduction from 7 – 10 days of

therapy to 5 days of therapy) did not raise the same or new safety issues involved with approving a new indication. Further, post-marketing adverse event reporting showed disturbances in glucose homeostasis particularly in diabetic patients, a population at increased risk for skin and skin structure infections.

Summary

In summary, the Tequin USSSI indication has involved a complicated submission history and complex regulatory process. The pattern of amending pending applications with new studies has led to a significant delay in approving final printed labeling that reflects the Division's level of concern regarding gatifloxacin's effect on glucose homeostasis and QT prolongation as well as delaying approval of the USSSI indication. This concern was brought to the attention of BMS and the need to bring to closure action on the indication and safety information emphasized. As a result, BMS and the Division successfully negotiated final labeling based on the labeling submitted by BMS on August 23, 2002. An approval letter for administrative NDAs 21-404 and 21-405 (USSSI indication), for NDA 21-061/S-010 and NDA 21-062/S-011 (QT prolongation labeling supplements), and for NDA 21-061/S-016 and NDA 21-062/S-017 (glucose homeostasis labeling supplements) issued on October 17, 2002.

{See appended electronic signature page}

Diana Willard
Regulatory Health Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Diana Willard
10/23/02 09:48:55 AM
CSO

Renata Albrecht
10/28/02 03:45:19 PM
MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE #

FACSIMILE TRANSMITTAL SHEET

DATE: October 11, 2001

To: Joan C. Fung-Tomc, Ph.D.	From: Diana M. Willard
Company: Bristol-Myers Squibb Company Wallingford, CT 06492	Division of Special Pathogen and Immunologic Drug Products
Fax Number: 203-677-7867	Fax Number: 301-827-2475
Phone Number: 203-677-6370	Phone Number: 310-827-2127

Subject: NDA 21-404 and NDA 21-405

Total no. of pages including cover: 3

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2336. Thank you.

NDA 21-404
NDA 21-405
October 11, 2001

Please refer to your June 29, 2001 submissions for NDAs 21-404 and 21-405 for Tequin. We have the following requests/comments regarding these submissions:

1. In Volume 9, pages 188 and 206, you state that subject 2367-2 died of unknown causes on . Several attempts were made to obtain further information on the circumstances surrounding this death but the study site did not comply.

Have you been able to obtain any further information on this subject?

- 2) In Volume 9, page 213, you state that 19 subjects discontinued study therapy due to adverse reactions (AEs), yet no information was provided on these AEs. Case report forms were provided for these subjects, yet they were not included in the discussion of AEs resulting in study drug discontinuation.

Do you have further information on the AEs that led to study drug discontinuation in these 19 subjects?

- 3) In Volume 9, pages 218 and 219, section 11.5, you state that of the four unintended pregnancies in Protocol AI420-088, two aborted while two opted to carry the pregnancies to term. The submission states that "The investigator will provide follow-up information regarding the course of the two pregnancies, including perinatal and neonatal outcome."

In Volume 10, page 198, you state that there was a report (10428381/US) of exposure to gatifloxacin during pregnancy and that the outcome of the pregnancy was unknown at the time of the submission.

Do you have follow-up information on these three pregnancy exposures?

- 4) In Volume 10, page 200, you list three deaths (10305183/US, 10520997/US, and 10485399/US) lacking specific causes of death.

Please provide the basis for determining the relationship of these deaths to the study drug.

- 5) In Volume 10, pages 204 and 206, Subject 10388163 is listed as having hyperglycemia (page 204) and hypoglycemia (page 206) but the blood glucose given for both events is 335 mg/dl.

Please clarify this inconsistency.

NDA 21-404
NDA 21-405
October 11, 2001

If you have any questions regarding this facsimile transmission or would like to request a teleconference to discuss these issues, please contact me at (301) 827-2485.

Diana Willard
Regulatory Health Project Manager
Division of Special Pathogen and
Immunologic Drug Products

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

/s/

Diana Willard
10/11/01 10:00:46 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID # D010228
DATE: August 13, 2001
TO: Mark Goldberger, M.D., M.P.H., Director
Division of Special Pathogen and Immunologic Drug Products,
HFD-590
THROUGH: Kathleen Uhl, M.D., Acting Director -/S/- August 13, 2001
Division of Drug Risk Evaluation II, HFD-440
FROM: Sarah J. Singer, R.Ph., Safety Evaluator
Division of Drug Risk Evaluation II, HFD-440
SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW
Drugs: Moxifloxacin (Avelox®) and gatifloxacin (Tequin®)
Reactions: Comparison of selected events reported postmarketing

THIS DOCUMENT CONTAINS INFORMATION FROM IMS HEALTH, INC. THE INFORMATION IS COPYRIGHTED AND CANNOT BE USED OUTSIDE THE FDA WITHOUT PRIOR PERMISSION FROM IMS HEALTH, INC.

Although the postmarketing information in this document is presented as a comparison of moxifloxacin and gatifloxacin, **EXTREME CAUTION** must be used in the interpretation of any quantitative data and reporting rates.

Numerous factors influence reporting to a spontaneous reporting system and can vary between products.

NO CONCLUSIONS AS TO THE RELATIVE SAFETY OF THE TWO DRUGS SHOULD BE MADE SIMPLY FROM A COMPARISON OF THE NUMBERS OF REPORTS OR THE REPORTING RATES.

TABLE OF CONTENTS

	page
I. Utilization data.....	3
II. Total counts from AERS.....	4
III. Literature.....	4
IV. Deaths.....	5
V. Pediatric cases.....	7
VI. Events by body system	
A. General body	
1. Anaphylaxis/angioedema.....	7
2. Drug-drug interactions.....	9
3. Overdose.....	10
B. Cardiovascular	
1. Torsade de pointes and surrogates.....	11
2. Ventricular arrhythmias/cardiac arrest/sudden death.....	15
3. Atrial fibrillation.....	18
C. Digestive	
1. Hepatic events.....	18
2. Pancreatitis.....	20
3. Gastrointestinal bleeding.....	21
D. Hematologic.....	22
E. Metabolic/endocrine	
1. Glucose abnormalities.....	25
2. Hypokalemia.....	29
F. Neurologic	
Convulsions.....	30
G. Renal.....	32
H. Respiratory.....	34
I. Skin	
1. Bullous conditions.....	35
2. Vasculitis.....	36
J. Special senses	
1. Hearing loss.....	36
2. Loss of taste and/or smell.....	37
VII. Summary/Recommendations.....	38

I. UTILIZATION DATA¹:

The IMS HEALTH, INC. NPA PlusTM database indicates that approximately [redacted] prescriptions for oral Avelox® and [redacted] prescriptions for oral Tequin® were filled by retail pharmacies (chain, independent, food store and mail order) in the United States between January 2000 and March 31, 2001.

Because moxifloxacin is not yet available in an IV formulation, OPDRA has been informed anecdotally that hospitals are less likely to include it in their formularies than gatifloxacin. The IMS HEALTH, INC. Provider PerspectiveTM database was queried for the purchases of each drug by U.S. inpatient facilities between January 2000 and March 31, 2001. During that time period, more than [redacted] tablets and [redacted] of Tequin® were purchased, versus less than [redacted] tablets (and of course no injectables) of Avelox®. Although purchases are a less accurate measure of utilization than actual prescriptions, these data do indicate that gatifloxacin is being used in U.S. inpatient settings to a greater degree than moxifloxacin.

¹ INFORMATION FROM IMS HEALTH, INC. IS COPYRIGHTED AND CANNOT BE USED OUTSIDE THE FDA WITHOUT PRIOR PERMISSION FROM IMS HEALTH, INC.

Although gatifloxacin has much higher utilization than moxifloxacin in the United States, the situation may be different worldwide. The Bayer Corporation has informed DSPIDP that more than _____ prescriptions have been filled for moxifloxacin worldwide. To date, the only countries aside from the United States which have approved gatifloxacin are Mexico, Brazil, and Argentina; the amount of gatifloxacin used in those countries is not known by OPDRA, but very few adverse event reports have been received from them. During its review of the new indication for gatifloxacin, DSPIDP could ask Bristol-Myers Squibb to provide worldwide utilization information.

OPDRA has also obtained data from IMS HEALTH, INC. regarding the relative use of moxifloxacin and gatifloxacin in different patient populations. The National Disease and Therapeutic Index™ database was queried for the gender and age breakdown of patients for whom either drug was ordered during a U.S. office practice visit in calendar year 2000. More than _____ of the use of both drugs was in patients 19 to 64 years of age, and most of the remainder was in patients aged 65 and over; less than _____ of patients receiving either drug were under 18 years of age. Both drugs were used approximately equally in males and females.

II. TOTAL COUNTS FROM THE ADVERSE EVENT REPORTING SYSTEM:

The FDA's Adverse Event Reporting System (AERS) database was searched April 13, 2001 for all events reported with moxifloxacin or gatifloxacin as a suspect drug. The searches found 1209 cases for moxifloxacin and 531 cases for gatifloxacin; these raw numbers contain duplicate reports and causality has not been assessed. Numerous factors, such as publicity and the diligence with which a company pursues reports, can influence spontaneous reporting rates. It is unwise to compare numbers of events between drugs even when the relative utilization is known.

Bristol-Myers Squibb waiver:

An additional confounding factor in a comparison between the numbers of reports for gatifloxacin and moxifloxacin is that Bristol-Myers Squibb has filed a waiver not to submit report forms for Tequin®-associated nonserious labeled events. The company merely lists those events in their periodic reports for the drug. Bayer has not filed such a waiver for Avelox®, so presumably the total AERS counts for Tequin® would be lower than those for Avelox® even if both drugs were suspect in the same numbers of adverse events. AERS contains 216 (≈41% of the total) periodic reports for Tequin® versus 584 (≈48%, not an appreciably higher percentage) for Avelox®. The emphasis in this document is on serious unlabeled events, however, for which no waivers are possible.

III. LITERATURE:

PubMed was searched on May 1, 2001 for any citations relating to moxifloxacin or gatifloxacin. A total of 217 citations were found for moxifloxacin and 148 for gatifloxacin, but most dealt with in vitro microbiologic studies and the remainder were primarily review articles or summaries of clinical trials which had been available at the time the drugs were approved.

Two recent articles on adverse events were found for moxifloxacin. Tachycardia is a labeled event for moxifloxacin.

1. Siepmann M, Kirch W. Tachycardia associated with moxifloxacin. *BMJ* 2001;322:23.
2. Carrion Valero F, Facila Rubio L, Marin Pardo J. [Syncope after administration of moxifloxacin]. *Arch Bronconeumol* 2000;36:603-4.

One article was found on a gatifloxacin adverse effect. The first author of the publication has co-authored another publication with three employees of Bayer².

Iannini PB, Circiumaru I. Gatifloxacin-induced QT prolongation and ventricular tachycardia. *Pharmacotherapy* 2001;21:361-2.

IV. DEATHS:

At the DSPIDP Administrative Rounds meeting on June 18, 2001, the Director of the Office of Drug Evaluation IV (ODE-IV) requested that OPDRA provide reporting rates for deaths and sudden deaths (see pp.16-17) of all the fluoroquinolones to get a sense of how the two new products compare with those already on the market.

OPDRA presented numerous caveats which must be considered in a reporting rate comparison:

1. The numerators are raw counts from AERS and probably include duplicates. Duplicate cases are probably more frequent with moxifloxacin than the other drugs because Bayer assigns multiple numbers to each case, making automatic linking of followups in AERS more problematic than with other companies' products. Case-linking was done manually prior to the introduction of AERS at the end of 1997, so the percentage of nonlinked cases should be lower for Cipro® (another Bayer product) than for Avelox®.
2. The numerators are unevaluated counts from AERS, and the relationship of the drugs to the deaths is unknown. For many of these products, which can be used in serious infections, deaths are frequently stated to have been due to the patient's underlying illness.
3. Numerous factors, including publicity and company diligence, influence reporting to a spontaneous reporting system such as AERS. In addition, deliberate attempts to negatively influence reporting for competitor products have been suspected with certain of the fluoroquinolones.
4. Reporting rates tend to be higher in the first year or two after approval of a new product.
5. Reporting for all products has increased over the years.
6. The denominators are based on U.S. outpatient prescription data only and may not truly represent the relative use of the products.
7. The numerators and denominators are not strictly comparable, although both are restricted to U.S. data. The numerators may include inpatients and patients who received the drugs intravenously. The denominators represent only outpatients receiving oral product.

EXTREME CAUTION must be used in the interpretation of reporting rates.

NO CONCLUSIONS AS TO THE RELATIVE SAFETY OF DRUGS SHOULD BE MADE SIMPLY FROM A COMPARISON OF REPORTING RATES.

Despite these caveats, it was recognized that the relative benefits of the newer products, with their broader indications, should be evaluated against any higher risk they might also convey. The following tables thus provide the comparisons requested by the ODE-IV Director. Table 1 compares all the products in their first year postmarketing, because of caveat #4 above; however, because of caveat #5, the reporting rates for the oldest products may be lower anyway. Table 2 compares the drugs since approval through the end of calendar year 2000. The gatifloxacin and moxifloxacin rows are highlighted.

² Iannini PB, Kubin R, Reiter C, Tillotson G. Reassuring safety profile of moxifloxacin [letter]. *CID* 2001;32:1112-4.

TABLE 1: FIRST-YEAR U.S. DEATH REPORTING RATE FOR FLUOROQUINOLONES

DRUG	APPROVAL DATE	U.S. ORAL PRESCRIPTIONS IN FIRST YEAR ³	TOTAL U.S. DEATHS IN FIRST YEAR ⁴	FIRST-YEAR DEATH REPORTING RATE PER PRESCRIPTIONS
Ciprofloxacin	10/87		16	5.6
Enoxacin	12/91		0	---
Gatifloxacin	12/99		17	9.4
Grepafloxacin	11/97		2	7.4
Levofloxacin	12/96		2	1.5
Lomefloxacin	2/92		4	1.4
Moxifloxacin	12/99		14 ⁵	16.6 ⁵
Norfloxacin	10/86		14	12.7
Ofloxacin	12/90		10	8.6
Sparfloxacin	12/96		0	---
Trovafoxacin/ alatrofloxacin	12/97		85 ⁶	67.5 ⁶

TABLE 2: U.S. DEATH REPORTING RATE THROUGH 2000 FOR FLUOROQUINOLONES

DRUG	APPROVAL DATE	U.S. ORAL PRESCRIPTIONS SINCE APPROVAL THROUGH 2000 ³	TOTAL U.S. DEATHS REPORTED THROUGH 2000 ⁴	DEATH REPORTING RATE PER PRESCRIPTIONS
Ciprofloxacin	10/87		180	1.4
Enoxacin	12/91		2	23.8
Gatifloxacin	12/99		18	9.4
Grepafloxacin	11/97 (withdrawn 10/99)		3	7.3
Levofloxacin	12/96		107	5.2
Lomefloxacin	2/92		9	2.2
Moxifloxacin	12/99		14 ⁵	16.6 ⁵
Norfloxacin	10/86		36	2.2
Ofloxacin	12/90		108	5.3
Sparfloxacin	12/96		4	39.2
Trovafoxacin/ alatrofloxacin	12/97 (use restricted 6/99)		216 ⁶	92.7 ⁶

³ U.S. oral outpatient prescriptions from retail pharmacies. Data obtained from the IMS HEALTH, INC. NPA Plus™ database; the information is copyrighted and cannot be used outside the FDA without prior permission from IMS HEALTH, INC. Data collection methods have changed over the years so the older and newer data are not strictly comparable.

⁴ Raw, unevaluated counts from AERS. May include duplicate, study, and literature reports; causality has not been assessed. Cases are included even if they occurred in inpatients or patients being treated with iv drug, so the numerators and denominators are not strictly comparable.

⁵ More duplicate cases in AERS than with the other products; see caveat #1 on p.5.

⁶ Trovan® death counts were heavily inflated by "hearsay" reports.

V. PEDIATRIC CASES (AGES 0-17):

AERS was searched for any moxifloxacin or gatifloxacin case with a stated patient age of zero through 17 years.

Only four unduplicated cases were found for moxifloxacin; all of the patients were at least 14 years of age. Two were reports of anaphylactoid reactions occurring shortly after the initial intake of moxifloxacin in patients with no known history of quinolone use. There were also two poorly documented cases of a 14-year-old who experienced a panic attack and a 15-year-old who developed gangrene after being treated for a wound which required stitches.

Only two cases were found for gatifloxacin, both in adolescent girls being treated for sinusitis. An 11-year-old with a history of Lyme disease developed nausea, sore throat, dizziness, weakness, and lethargy two days after starting gatifloxacin; and a 14-year-old developed muscle cramping, shoulder pain, and "felt weird" after one dose of gatifloxacin.

VI. EVENTS BY BODY SYSTEM

A. GENERAL BODY:

1. ANAPHYLAXIS/ANGIOEDEMA:

Shortly after the approval of moxifloxacin, Dr. Meyerhoff became concerned about the many cases of anaphylaxis being reported for this drug. OPDRA has provided numerous updates of the AERS counts of such events, compared with other fluoroquinolones at equivalent times postmarketing. The most recent was a document dated March 10, 2001 (PID D010067).

Additional wording has recently been added to the Avelox® label under **WARNINGS** and **Post-Marketing Adverse Event Reports** indicating that anaphylactic reactions and anaphylactic shock have been reported in association with the drug.

Dr. Meyerhoff remains concerned, however, and requested an evaluation of AERS reports of angioedema. The cases of anaphylaxis were also reviewed to see if additional information could be gleaned from hands-on analysis.

Table 3 summarizes relevant information on the cases from AERS⁷. Duplicate cases were merged for this analysis, so the counts are not distorted. Cases reported as both angioedema and anaphylaxis are listed only under anaphylaxis.

⁷ Because of Bristol-Myers Squibb's waiver related to nonserious labeled events (see p. 4), relevant Tequin® cases have not been submitted to AERS. Review of the company's periodic reports found the following events in the line listing of unsubmitted cases: anaphylactic reaction (1 case), facial edema (9 cases), tongue edema (3 cases). BMS considers anaphylaxis a labeled event for Tequin® even though it is only listed in a class-labeling section which does not mention Tequin® per se. Prior to labeling revisions adding anaphylaxis to the ADVERSE REACTIONS section of the Avelox® labeling, Bayer did not consider anaphylaxis a labeled event for the drug even though the Avelox® labeling contains the same class-labeling section.

**TABLE 3: ANAPHYLAXIS AND ANGIOEDEMA CASES
ASSOCIATED WITH MOXIFLOXACIN AND GATIFLOXACIN**

DRUG/EVENT (as reported)	AGE	SEX	SERIOUS ⁸	ONSET (after X doses)	SYMPTOMS MEETING OPDRA DEFINITION OF ANAPHYLAXIS ⁹	RELEVANT HISTORY ¹⁰
MOXIFLOXACIN ANAPHYLAXIS N = 42	N = 32 Range: 15-78 Median: 41	N = 36 F: 25 M: 11	N = 19 LT: 11 HO: 8	N = 37 1 st : 31 2 nd : 6	N listing symptoms: 32 Symptoms meeting OPDRA definition: 16	FQ exposure: 6 No FQ exposure: 5 Other allergies: 20 No allergy history: 2
MOXIFLOXACIN ANGIOEDEMA N = 58	N = 39 Range: 15-76 Median: 49	N = 53 F: 45 M: 8	N = 14 LT: 6 HO: 7 DS: 1	N = 47 1 st : 29 2 nd : 9 Other: 9	N listing symptoms: 58 Symptoms meeting OPDRA definition: 18	FQ exposure: 9 No FQ exposure: 5 Other allergies: 14 No allergy history: 5
GATIFLOXACIN ANAPHYLAXIS N = 23	N = 15 Range: 23-63 Median: 40	N = 17 F: 11 M: 6	N = 12 LT: 7 HO: 5	N = 15 1 st : 12 2 nd : 1 Other: 2	N listing symptoms: 12 Symptoms meeting OPDRA definition: 3	FQ exposure: 1 Other allergies: 9
GATIFLOXACIN ANGIOEDEMA N = 13	N = 7 Range: 22-77 Median: 39	N = 10 F: 8 M: 2	N = 5 LT: 2 HO: 3	N = 12 1 st : 7 2 nd : 3 Other: 2	N listing symptoms: 13 Symptoms meeting OPDRA definition: 4	Other allergies: 4 No allergy history: 1

The number of gatifloxacin cases of the two events in AERS is thus 36% of the moxifloxacin cases (36 for gatifloxacin vs 100 for moxifloxacin). It is difficult to determine if moxifloxacin cases of anaphylaxis/angioedema are being reported as a higher percentage of cases than they are for gatifloxacin. In AERS as a whole, the raw numbers of gatifloxacin cases are 44% of the moxifloxacin cases (531 vs 1209, respectively), but there are far more duplicate reports for moxifloxacin than for gatifloxacin in AERS because Bayer assigns multiple case numbers to its cases and automatic case-linking does not occur as readily, so the gatifloxacin cases may be an even higher percentage of the unduplicated cases. However, the effect of Bristol-Myers Squibb's waiver must also be considered; potentially up to 13 more cases of these events should be added to the gatifloxacin total (see footnote 7 on p.7).

The case characteristics for the two drugs are quite similar for most of the criteria tabulated above. The median age is similar and correlates with the ages in which the drugs are most used (see UTILIZATION DATA on pp.3-4). For both drugs, far more cases have been reported in females (78% of the cases in which gender was reported for moxifloxacin; 70% for gatifloxacin) even though the utilization of both drugs is approximately the same for males and females (see UTILIZATION DATA). The event was considered life-threatening in a similar percentage of cases (17% for moxifloxacin; 25% for gatifloxacin). Anaphylaxis/angioedema was stated to have occurred after a single dose of the fluoroquinolone in a majority of the cases for both drugs (60% for moxifloxacin; 53% for gatifloxacin).

The two differences between the drugs are: the percentage of cases meeting the OPDRA case definition of anaphylaxis (see footnote 9); and relevant history. Of the reports listing symptoms, only 28% of the gatifloxacin cases vs 38% of the moxifloxacin cases met the OPDRA definition. Fifteen of the moxifloxacin cases mentioned a history of fluoroquinolone exposure vs only one of the gatifloxacin cases. Ten of the moxifloxacin cases specifically stated that the patient had no history of fluoroquinolone exposure; none of the gatifloxacin cases mentioned a lack of exposure. It is impossible to determine, however, if these are true differences in the cases or if they result from better questioning of reporters by Bayer safety personnel. (Similar percentages for both drugs reported a history of allergies.)

⁸ Serious by regulatory definition. There were no fatal cases; the only serious outcomes listed on the reports were life-threatening (LT), hospitalization (HO), and disability (DS).

⁹ OPDRA has used a case definition for anaphylaxis in which cases were included even without a diagnosis of anaphylaxis if at least one listed event from any two of the three following body systems was reported: (1) CUTANEOUS: angioedema, urticaria; (2) CARDIOVASCULAR: hypotension, shock; (3) RESPIRATORY: apnea, asthma, dyspnea, laryngeal edema, hypoventilation, laryngismus, respiratory disorder, stridor.

¹⁰ "FQ exposure" means previous exposure to any fluoroquinolone.

2. DRUG-DRUG INTERACTIONS:

All AERS reports in which moxifloxacin or gatifloxacin were stated to have (possibly) interacted with another drug were reviewed. There were only two drug classes in which an interaction was reported in more than one patient: digitalis glycosides and coumarin anticoagulants¹¹.

Digitalis glycosides:

The current Avelox® labeling cites clinical pharmacology studies which showed that moxifloxacin had no clinically significant effect on digoxin kinetics, and digoxin did not affect the pharmacokinetics of moxifloxacin. The clinical pharmacology studies mentioned in the Tequin® labeling showed that concomitant administration of gatifloxacin and digoxin did not significantly alter the pharmacokinetics of gatifloxacin, but a modest increase in digoxin concentrations was observed in three of 11 patients.

AERS contained two cases, both from Germany, in which elderly female patients experienced events thought to be possibly related to a moxifloxacin-digitalis interaction. One of the reports (AERS # 3458178) stated that the patient had a digitalis overdose despite a digitoxin dose of 0.2 mg/day; however, the report was confusing and the highest digitoxin level listed, 45.6 ng/ml, may have occurred prior to the start of moxifloxacin. The other report (AERS # 3438575) stated that a physician suspected a possible interaction with digoxin when his patient developed nausea and dizziness shortly after starting moxifloxacin, but the blood sample was not usable so no digoxin plasma level was obtained. Nausea and dizziness are events which have been associated with moxifloxacin monotherapy.

AERS also contained a report (AERS # 3555150) of a possible interaction between digoxin and gatifloxacin. Within days of starting gatifloxacin, the patient presented to her physician complaining of dizziness, nausea, vomiting, and malaise. Her heart rate was 40 and her digoxin serum level was 3.4 (normal range listed as 0.8 to 2.0—units not given). The patient was also receiving amiodarone; amiodarone is labeled for interactions with digoxin.

Coumarin anticoagulants:

Interactions with coumarin anticoagulants occur with many anti-infective agents, including fluoroquinolones. The current Avelox® labeling lists "prothrombin time increase" as having been reported in clinical trials. The Tequin® labeling does not mention prothrombin time but states that ecchymosis and epistaxis occurred in clinical trials. The **Drug Interactions** section of the labeling for both drugs states that no significant pharmacokinetic interactions with warfarin were observed in clinical pharmacology studies, but prothrombin time or other suitable coagulation test should be closely monitored since other quinolones have been reported to enhance the effects of warfarin or its derivatives.

AERS cases reporting a warfarin interaction with either moxifloxacin or gatifloxacin were reviewed. In addition, AERS was searched for any case in which warfarin was administered concomitantly with either drug; that printout was reviewed and any case reporting a coagulation test abnormality or bleeding event (even if no interaction was mentioned) was also retrieved for hands-on analysis. Table 4 presents a summary of the cases.

¹¹ Dr. Meyerhoff has suggested the possibility of an interaction with non-sedating antihistamines; see *Syncope or loss of consciousness* on p.14.

TABLE 4: INTERACTIONS WITH COUMARIN ANTICOAGULANTS

	MOXIFLOXACIN	GATIFLOXACIN
Number of unduplicated cases	11	13
Age range (years)	68-90 (N=10)	58-89 (N=11)
Gender	M 5, F 4 (N=9)	M 2, F 10 (N=12)
Serious?	Life-threatening 1 Hospitalization 3	Hospitalization 3
Bleeding?	N=4 GI bleed 2 Hematoma 1 Hematuria 1	N=3 Petechiae 2 Abdominal bleed 1 GI bleed 1 Epistaxis 1

Most of the reports provided too little information to make an assessment of the role of the fluoroquinolone (for example, the length of time on warfarin and whether the patient was stable prior to the initiation of moxifloxacin or gatifloxacin were rarely stated). Additional reports were confounded by concomitant medications known to interact with warfarin, with no indication as to the dates of administration of those drugs.

However, there were four moxifloxacin and two gatifloxacin cases in which the patients had been stable on warfarin prior to the quinolone¹². Concomitant medications were chronic drugs, except that one patient had been given one dose of ceftriaxone and another had been given two doses of levofloxacin (both labeled for causing alterations in prothrombin time). The increased PTs/INRs were noted within days of starting moxifloxacin or gatifloxacin. One patient developed a hematoma, another had hematuria, and a third had an unspecified abdominal bleed; the three other patients apparently did not experience any bleeding episodes.

The best-documented case for each drug is presented briefly below.

AERS # 3529247, Mfr # 200002402, █████, 2000.

A 79-year-old female had been on warfarin for seven years with stable PTs/INRs. She had had coagulation tests performed three days before starting moxifloxacin and the results had been: PT 18.0, INR 2.2. She was given a 10-day course of moxifloxacin, was off the drug five days and then was given a prescription for another 10-day course. All other concomitant medications (atorvastatin, furosemide, amlodipine) were chronically administered. Eight days into her second course of moxifloxacin, she had routine lab work done and her PT was 39.5 with an INR of 9.77. She was asymptomatic and had no signs of bleeding. Her warfarin was held for three days.

AERS # 3494932, Direct report, █████, 2000.

An 87-year-old female had been stable on warfarin "for quite some time". Before starting gatifloxacin, her PT had been 14. The day after completing a 10-day course of gatifloxacin, she felt dizzy and went to the hospital. Her PT was 40 and an abdominal bleed was discovered. She was given a blood transfusion. The FDA contacted the reporter approximately one month after the event and was informed that the patient had improved. All her other medications (loratadine, probenecid/colchicine, spironolactone, amitriptyline, isosorbide, albuterol, amlodipine, and zaleplon) were chronic medications which were not discontinued.

3. OVERDOSE:

Moxifloxacin:

In June 2000, OPDRA contacted DSPIDP concerning three cases of Avelox® overdoses in which patients took five tablets at once. One of the reports specifically stated that the patient had misinterpreted the ABC pack, which at that time contained labeling stating "five tablets, once daily". In September 2000, the Medication Errors staff of OPDRA issued a consult (# 00-012-2) reviewing Bayer's proposed reconfiguration of the ABC Pack and other labeling changes.

¹² After the "data-lock" date for this document, one additional moxifloxacin case and two gatifloxacin cases were received. In the gatifloxacin cases it was not stated if the patients had been stable on warfarin prior to the start of the drug. However, the moxifloxacin patient had been stable, developed hematuria from a bleeding vein on the bladder within two days of starting moxifloxacin, and his INR had gone from approximately 1.8 to 3.84.

OPDRA recommended further labeling revisions but concluded that the company's proposed changes would reduce the chances of patients taking all five tablets at once.

All moxifloxacin cases of overdose received as of April 13, 2001 were reviewed. AERS contained 11 additional unduplicated cases of overdose unrelated to the ABC Pack, most involving patients who had taken two tablets less than 24 hours apart. All of the events were nonserious; only nausea and dizziness were reported in more than one case. One patient had ECGs measured twice a day for three days but all were normal and showed no QT prolongation.

Gatifloxacin:

AERS contained only four reported cases of gatifloxacin overdose, two of which were asymptomatic. Another patient (an elderly female weighing 108 lb) developed profound thrombocytopenia and it was determined that, based on her creatinine clearance, she should have received half doses of gatifloxacin. However, it was later decided that her platelet decrease was secondary to DIC from sepsis, because there was no improvement in platelet counts after her gatifloxacin regimen was changed.

The fourth case (AERS # 3123544) is more concerning. An 88-year-old female received three doses of gatifloxacin within 24 hours and became comatose. It was initially thought that the event was a reaction to her fentanyl transdermal patch, but removal of the patch and administration of naloxone did not result in improvement. She improved somewhat within 12 hours of her last gatifloxacin dose and was completely oriented by the next morning. The possibility of a stroke was entertained.

B. CARDIOVASCULAR:

1. TORSADE DE POINTES AND SURROGATES:

Potential torsade de pointes has been a concern of DSPIDP since before the approval of both moxifloxacin and gatifloxacin, because moxifloxacin caused a mean QT prolongation of 6 msec and gatifloxacin 3 msec in clinical trials. The cases of torsade (see below) reported to AERS in association with moxifloxacin and gatifloxacin, while temporally suggestive of a role for the two drugs in their etiology, occurred in patients who had multiple risks for such events. Given the wide use of both drugs, a lack of less confounded cases is reassuring.

AERS reports of moxifloxacin- and gatifloxacin-associated sudden death and syncope (events frequently identified as torsade surrogates) were also reviewed. Although AERS contained more cases of torsade associated with gatifloxacin than with moxifloxacin, the reverse is true for the two surrogate events. However, Dr. Meyerhoff has suggested that anaphylaxis rather than torsade might be the cause of the sudden deaths and syncope.

Moxifloxacin torsade cases:

In March 2001, OPDRA provided DSPIDP a document (PID D010067) summarizing moxifloxacin-associated cases of all types of ventricular arrhythmias reported to AERS; at that time, there were two unduplicated cases of torsade de pointes, both of which were quite confounded. Since that document, an additional case of torsade has been received. The three cases (AERS # 3445074, 3613365, 3626034), all from Europe, are summarized briefly below:

All three patients were elderly females (78, 83, and 84 years of age). Weight and height were only reported in one case (130 lb, 5'2"). All three patients had cardiac histories including arrhythmias and cardiac "insufficiency" or failure. One patient was receiving amiodarone. One had been hypokalemic and had an elevated digitoxin level two days before starting moxifloxacin; digitoxin had been stopped for one day and KCl had been infused, but no blood levels had been

obtained before starting moxifloxacin. Electrolytes were not reported on another case, but the patient was receiving hydrochlorothiazide with no mention of potassium supplementation. The third patient, however, was stated to have had normal electrolytes the day torsade occurred.

In all three cases, torsade was temporally related with moxifloxacin therapy; time to onset was one to four days after starting moxifloxacin, which was the only new drug in all three cases. The reports state that torsade did not recur after moxifloxacin was withdrawn. However, followup on two of the cases stated that sick-sinus syndrome and a "bradycardia-tachycardia syndrome" were later diagnosed and both patients received pacemakers about two weeks after their torsade episodes.

The QT interval was determined in all three cases. In the first case, baseline QT was 490 msec; it was stated to also have been 490 msec immediately after torsade occurred, but 510 msec earlier that day. No baseline QT was provided in the second case; QTc was 497 msec the day after the torsade episode and 700 msec three days later. In the third case the patient's QT interval was 440 msec the day of her torsade episode. The last two cases were the patients who later received pacemakers.

Gatifloxacin torsade cases:

The FDA has received eight unduplicated cases of torsade de pointes and a case reported as "polymorphic ventricular tachycardia with marked QT prolongation" associated with gatifloxacin use. All are U.S. cases. Three were reported by a physician who has an affiliation with Bayer and one of the three has been published (see LITERATURE on pp.4-5).

Age was reported in eight of the nine total cases; seven patients were elderly (66 to 85 years of age, median = 81 years). The lone exception was a 47-year-old with a history of congenital heart block, malfunctioning pacemaker, and artificial heart placement. There were seven females (78%) and two males. Weight was reported in four cases and ranged from 126 to 196 lb; height was not reported in any of the cases. Six of the patients had cardiac histories including coronary disease, arrhythmias, and/or heart failure; another patient had hypertension and the remaining two were on amlodipine and atenolol, respectively, for unstated indications. One patient was receiving sotalol but had been stable on it with a QTc of 428 msec, and another had been on amiodarone for an unstated period. A third patient was given a single IV dose of amiodarone shortly after her first dose of gatifloxacin and just prior to the onset of torsade. Electrolytes were reported in six cases: potassium was low in three and WNL in three; magnesium was low in one and WNL in three.

Torsade was temporally associated with gatifloxacin therapy in all eight of the nine cases for which that information was given (time to onset one to three days after starting the drug). Gatifloxacin was stated to be the only new therapy in five of the cases. The drug was administered IV in three cases and orally in four; route was not reported in two cases. Fluconazole is a confounding factor in two of the cases; it was stated to have been introduced two days prior to gatifloxacin in one of the cases and was considered co-suspect.

The QTc interval was reported in five cases. Baselines ranged from 350 to 443 msec (n=3) and event QTc ranged from 418 to 690 msec. The reporter with the Bayer affiliation provided the FDA the patients' ECGs after he was contacted by the Agency.

Sudden death:

AERS coders have been instructed not to make assumptions; they do not code a fatal case as a sudden death unless the reporter specifically used that terminology. This OPDRA Safety Evaluator, who is assigned gatifloxacin and moxifloxacin, has seen cases in her AERS inbox which she considered sudden death cases even though they were not coded that way and would not have been retrieved in a search for that event.

During a CDER course entitled "QT Prolongation and Drug Development", Dr. Douglas Throckmorton of HFD-110 (DCRDP) indicated that he had developed criteria for "sudden death". When contacted by this Safety Evaluator, he sent the criteria as personal correspondence: (1) if the death was witnessed, the patient should go from alert to comatose/dead within a few seconds; and (2) if the death was unwitnessed (i.e., found dead in bed), the death would be considered sudden if no information to the contrary existed. Dr. Throckmorton's criteria were used to evaluate the cases which had not been coded as sudden deaths. Based on a standard medical reference¹³, cases were also included if they occurred within 24 hours of starting therapy in patients without acute symptomatology of heart disease. All cases were included if they were described as sudden deaths by the reporters; these were the cases that had been coded as sudden deaths.

Using these criteria, AERS contained 12 cases of sudden death associated with moxifloxacin and six associated with gatifloxacin¹⁴. Eight of the moxifloxacin and one of the gatifloxacin patients were found dead, three of the moxifloxacin and four of the gatifloxacin cases were reported as sudden deaths, and one each were cases in which patients with no acute cardiac symptomatology died within 24 hours of starting therapy with the fluoroquinolone (and it was the only new drug).

The patients were somewhat younger than the torsade patients; ages ranged from 25 to 88 years for moxifloxacin (median = 77 years) and 51 to 68 years for gatifloxacin (median = 65 years). There was a higher percentage of males among the gatifloxacin cases: four (33%) of the moxifloxacin patients and five (83%) of the gatifloxacin patients were male.

Death occurred within a day of starting moxifloxacin in eight of the 12 cases and within a day of starting gatifloxacin in three of the six cases. Two moxifloxacin patients died within three hours of starting the drug, which would support Dr. Meyerhoff's theory that anaphylaxis was the cause in those cases.

Possible confounding factors are listed in Table 5.

TABLE 5: CONFOUNDING FACTORS IN SUDDEN DEATH CASES

		MOXIFLOXACIN	GATIFLOXACIN
HISTORY			
	Cardiovascular disease (not hypertension)	4	5
	Chronic lung disease	3	1
	Alcoholism	3	
	Smoking	2	2
	Obesity	2	
CONCOMITANT MEDICATIONS LABELED FOR VENTRICULAR ARRHYTHMIAS			
	Digitalis glycoside	2	1
	Theophylline	2	
	Haloperidol	1	
	Amiodarone		1
	Allopurinol		1
	Torsemide		1

¹³ Berkow R, Fletcher AJ, eds. The Merck manual of diagnosis and therapy. 16th ed. Rahway, NJ: Merck & Co., Inc. 1992;520.

¹⁴ After the "data-lock" date for this document, two additional moxifloxacin sudden death cases were received.

Syncope or loss of consciousness:

The labeling for both moxifloxacin and gatifloxacin lists dizziness and vertigo as having occurred in clinical trials. AERS was searched for all cases coded SYNCOPe or LOSS OF CONSCIOUSNESS for either drug; cases would also have been retrieved if they mentioned "fainting", "passing out", or "blacking out". Retrieved cases which were previously presented under **TORSADE DE POINTES** above were excluded from this analysis.

AERS contained 56 unduplicated cases of these events for moxifloxacin and 23 for gatifloxacin. Most of the reports contained minimal information and it would be difficult to reach any conclusions about the possible etiology of the event.

The patients were younger than in the torsade cases. Age was reported in 46 of the moxifloxacin cases and ranged from 17 to 90 years (median = 58 years). It was reported in 19 of the gatifloxacin cases and ranged from 19 to 91 years (median = 67 years).

Gender was reported in 49 of the moxifloxacin cases: 32 females (65%), 17 males. It was reported in 22 of the gatifloxacin cases: 17 females (77%), 5 males. Weight was reported in 18 of the moxifloxacin cases (median 153 lb) but only four of the gatifloxacin cases (median 111 lb).

Electrocardiographic findings were obtained shortly after the event in ten of the moxifloxacin cases; only four patients had prolonged QT intervals. Two of the three ECGs obtained in gatifloxacin patients showed prolonged QT intervals.

Dr. Meyerhoff suggested that syncope could have resulted from an anaphylactic reaction as well as from a cardiac event. Among the moxifloxacin cases, four were reported as anaphylactic events and an additional seven included signs and/or symptoms suggesting such an event (laryngeal or facial edema, urticaria, pruritus, tingling, and/or rash). Among the gatifloxacin cases, one was reported as anaphylaxis and three included signs and/or symptoms of anaphylaxis. One of the three was thought to be a case of serum sickness, which the patient had experienced with another antibiotic.

Four of the moxifloxacin cases were reported as vasovagal syncope, for reasons not entirely clear in three of the cases. The diagnosis was reached in one of the four, however, because the patient experienced gastrointestinal distress just prior to the syncope and had an ECG which showed normal sinus rhythm.

Glucose abnormalities rather than a cardiovascular disorder may have been the precipitant of syncope in up to six of the cases. Hypoglycemia was reported to be the cause of the event in four of the gatifloxacin cases (none of the moxifloxacin cases). Hyperglycemia was the reported cause in one gatifloxacin case; one of the moxifloxacin patients was later discovered to have a glucose of 125 (units not given) but the reporter did not comment on the finding. See additional discussion under **GLUCOSE ABNORMALITIES** on pp.25-29.

The possibility that a drug interaction with a nonsedating antihistamine may have led to syncope was raised by Dr. Meyerhoff, who noticed that two reports of moxifloxacin-associated syncope occurred in patients on fexofenadine (one of the patients had a QTc of 446 msec). None of the 54 other moxifloxacin patients experiencing syncope had received fexofenadine; one of the 23 gatifloxacin patients had. In addition, three moxifloxacin patients and one gatifloxacin patient were on loratadine, and the gatifloxacin patient was stated to have had a prolonged QT interval. Cetirizine was not mentioned in any of the cases. OPDRA has previously sent consult documents to HFD-570 (DPADP) about the possible cardiac effects of nonsedating antihistamines currently on the market; the most recent was a document dated May 23, 2001 (PID D010020). To date, however, the division is not convinced that these drugs have QT effects. It is not clear if these cases represent interactions between the fluoroquinolones and the nonsedating antihistamines, or just a syncopal effect of the fluoroquinolones.

2. VENTRICULAR ARRHYTHMIAS/CARDIAC ARREST/SUDDEN DEATH:

Moxifloxacin-gatifloxacin-grepafloxacin comparison:

Dr. Meyerhoff requested the number of unduplicated cases of ventricular arrhythmias and cardiac arrest reported for grepafloxacin compared with moxifloxacin and gatifloxacin. Grepafloxacin was withdrawn from the market by the sponsor in October 1999, supposedly because of cardiac toxicity; however, its original license-holder claims that the drug is not cardiotoxic and is requesting a return to the market.

AERS was searched for all three drugs using the grouping term VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST. Duplicate or miscoded cases and cases of cardiac or cardiopulmonary arrest secondary to the patient's underlying disease (such as sepsis or pneumonia) were excluded. Then each case was entered into Table 6 only once starting at the top (i.e., a case of torsade de pointes resulting in cardiac arrest was entered only under torsade de pointes).

TABLE 6: VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST REPORTED WITH THREE FLUOROQUINOLONES

EVENT	MOXIFLOXACIN		GATIFLOXACIN		GREPAFLOXACIN	
	Domestic	Foreign	Domestic	Foreign	Domestic	Foreign
Torsade de pointes	0	3	8	0	2	0
Sudden death ¹⁵	4	3	2	3	0	1
Cardiac arrest	2	0	2	0	0	3
Ventricular fibrillation	2	1	0	0	0	0
Ventricular tachycardia	1	1	6	0	2	1
Ventricular arrhythmia unspecified	0	1	0	0	0	0
Premature ventricular contractions	4	3	2	0	1	1
TOTAL FOR DRUG	25		23		11	

As background for comparing the events reported with the drugs, Dr. Meyerhoff provided the information that grepafloxacin was used worldwide in [redacted] patients through October 1999 and that moxifloxacin has now been used in more than [redacted] patients. As stated under **UTILIZATION DATA** on pp.3-4, OPDRA has no information on the worldwide use of gatifloxacin but almost [redacted] outpatient prescriptions had been filled in the U.S. at the end of March 2001, and purchases of the drug by U.S. inpatient facilities have been substantial.

¹⁵ Only if coded as SUDDEN DEATH. Additional cases for gatifloxacin and moxifloxacin were found during Safety Evaluator inbox review and are included on pp.12-13 above.

Sudden death in all fluoroquinolones:

At the meeting during which she requested comparisons of all deaths among the fluoroquinolone class (see **DEATHS** on p.5), the ODE-IV Director also requested a comparison of sudden death reporting rates among the drugs.

Most of the same caveats that were provided for the death reporting rate comparison (see p.5) also apply to the comparison of sudden death reporting rates. Because the numbers are fewer, however, it was possible to review all the cases to eliminate duplicates. On the other hand, potentially relevant cases are not coded as SUDDEN DEATH unless described that way by reporters (see p.12).

The relevant caveats from p.5 are repeated below and the caveat related to coding is added.

1. Potentially relevant cases were not retrieved, because cases are not coded as SUDDEN DEATH unless described that way by reporters.
2. Numerous factors, including publicity and company diligence, influence reporting to a spontaneous reporting system such as AERS. In addition, deliberate attempts to negatively influence reporting for competitor products have been suspected with certain of the fluoroquinolones.
3. Reporting rates tend to be higher in the first year or two after approval of a new product.
4. Reporting for all products has increased over the years.
5. The denominators are based on U.S. outpatient prescription data only and may not truly represent the relative use of the products.
6. The numerators and denominators are not strictly comparable, although both are restricted to U.S. data. The numerators may include inpatients and patients who received the drugs intravenously. The denominators represent only outpatients receiving oral product.

EXTREME CAUTION must be used in the interpretation of reporting rates.

NO CONCLUSIONS AS TO THE RELATIVE SAFETY OF DRUGS SHOULD BE MADE SIMPLY FROM A COMPARISON OF REPORTING RATES.

Tables 7 and 8 present the reporting rate for sudden deaths during the first year postmarketing, and since approval through the end of 2000, for each drug. The gatifloxacin and moxifloxacin rows are highlighted. The numbers are small and the "new-drug reporting" phenomenon may have put gatifloxacin and moxifloxacin at a disadvantage in Table 8, if the drop in reporting rate for levofloxacin between Tables 7 and 8 can be used as an indicator. In addition, there has been increased knowledge about the QT-prolonging effects of the fluoroquinolones as well as publicity about those effects in the last few years, possibly causing higher reporting of sudden deaths for the two drugs introduced in that timeperiod (gatifloxacin and moxifloxacin).

TABLE 7: FIRST-YEAR U.S. SUDDEN DEATH REPORTING RATE FOR FLUOROQUINOLONES

DRUG	APPROVAL DATE	U.S. ORAL PRESCRIPTIONS IN FIRST YEAR ¹⁶	TOTAL U.S. SUDDEN DEATHS ¹⁷ IN FIRST YEAR	FIRST-YEAR SUDDEN DEATH REPORTING RATE PER PRESCRIPTIONS
Ciprofloxacin	10/87		0	---
Enoxacin	12/91		0	---
Gatifloxacin	12/99		2	1.1
Grepafloxacin	11/97		0	---
Levofloxacin	12/96		1	0.8
Lomefloxacin	2/92		0	---
Moxifloxacin	12/99		1	1.2
Norfloxacin	10/86		0	---
Ofloxacin	12/90		0	---
Sparfloxacin	12/96		0	---
Trovafloxacin/ alatrofloxacin	12/97		0	---

TABLE 8: U.S. SUDDEN DEATH REPORTING RATE THROUGH 2000 FOR FLUOROQUINOLONES

DRUG	APPROVAL DATE	U.S. ORAL PRESCRIPTIONS SINCE APPROVAL THROUGH 2000 ¹⁶	TOTAL U.S. SUDDEN DEATHS ¹⁷ REPORTED THROUGH 2000	SUDDEN DEATH REPORTING RATE PER PRESCRIPTIONS
Ciprofloxacin	10/87		2	0.02
Enoxacin	12/91		0	---
Gatifloxacin	12/99		2	1.1
Grepafloxacin	11/97 (withdrawn 10/99)		0	---
Levofloxacin	12/96		4	0.2
Lomefloxacin	2/92		0	---
Moxifloxacin	12/99		1	1.2
Norfloxacin	10/86		0	---
Ofloxacin	12/90		3	0.15
Sparfloxacin	12/96		0	---
Trovafloxacin/ alatrofloxacin	12/97 (use restricted 6/99)		0	---

¹⁶ U.S. oral outpatient prescriptions from retail pharmacies. Data obtained from the IMS HEALTH, INC. NPA Plus™ database; the information is copyrighted and cannot be used outside the FDA without prior permission from IMS HEALTH, INC. Data collection methods have changed over the years so the older and newer data are not strictly comparable.

¹⁷ If reported as sudden death. Additional cases for gatifloxacin and moxifloxacin were found during Safety Evaluator inbox review and are included on pp.12-13 above but not in this count. Duplicate cases have been merged. However, cases are included even if they occurred in inpatients or patients being treated with iv drug, so the numerators and denominators are not strictly comparable.

3. ATRIAL FIBRILLATION:

There were 14 unduplicated cases in AERS of atrial fibrillation diagnosed shortly after starting moxifloxacin, vs only three for gatifloxacin. Atrial fibrillation is not an event typically thought to be associated with anti-infective agents. In addition, the background incidence is high and rises with age¹⁸, making drug attribution difficult.

All but four of the moxifloxacin cases and all of the gatifloxacin cases occurred in patients over 65 years of age. One of the four younger patients had a history of palpitations and two others had hypertension. The fourth patient (51 years old) was stated to be previously healthy and not on any concomitant medications, but the report provides little additional information.

Dr. Meyerhoff suggested searching AERS for another fluoroquinolone and a non-fluoroquinolone antibiotic to see if atrial fibrillation had also been reported with them. The search found 16 cases for levofloxacin and 11 for cefuroxime; both numbers are raw, unevaluated counts but do indicate that such events are indeed reported to a certain extent with other anti-infectives.

C. DIGESTIVE:

1. HEPATIC EVENTS:

The current Avelox® labeling states that cholestatic jaundice and increased GGTP were seen in clinical trials; it has no mention of other hepatic events, even increased transaminases. The current Tequin® labeling states that increased ALT, AST, alkaline phosphatase, and bilirubin (no clinical events) were seen in clinical trials.

In March 20001, OPDRA provided DSPIDP a summary (PID D010134) of the 21 cases of gatifloxacin-associated hepatotoxicity which had been reported at that time. There were two cases of liver failure, but they were complex and the role of gatifloxacin was unclear. However, there were ten cases of hepatitis temporally associated with gatifloxacin use; several of the patients were young adults without complex histories. OPDRA recommended that a **Post-Marketing** subsection be added to the **ADVERSE REACTIONS** section of the Tequin® labeling and that hepatitis be included in the new subsection. DSPIDP hopes to incorporate those changes, and others resulting from this document, into new labeling which would be approved with the pending supplement for the new indication.

In April 2001, a meeting was held to discuss hepatic events seen with all fluoroquinolones. OPDRA provided the information that at least one clinical hepatic event is listed in the **ADVERSE REACTIONS** section of all the currently marketed drugs except gatifloxacin (the labeling for lomefloxacin and enoxacin lists hepatic necrosis, although only as a quinolone-class event). Of the drugs which do list a clinical hepatic disorder, moxifloxacin is the only one which does not include a hepatocellular event such as hepatitis or hepatic necrosis in the list. Many of the drugs also include a mention of hepatic events (either specifically for the particular drug, or as a class for quinolones or even "all antibiotics") under **PRECAUTIONS**.

At the April meeting, OPDRA also provided details of liver cases reported for moxifloxacin, as well as Table 9, which provides a comparison of the gatifloxacin and moxifloxacin cases (two additional gatifloxacin cases had been received).

¹⁸ Falk RH. Atrial fibrillation. N Engl J Med 2001;344:1067-78.

**TABLE 9: COMPARISON OF GATIFLOXACIN AND MOXIFLOXACIN
HEPATOTOXICITY CASES
AS OF 4/9/01¹⁹**

EVENT AS IN NARRATIVE (each case categorized once beginning at the top)	GATIFLOXACIN 23	MOXIFLOXACIN 22
LIVER FAILURE	3 (really 2): all fatal 1. Hepatorenal syndrome. Death from that or septic shock? 2. Turned out to be a GI bleed with some hepatomegaly & ↑ LFTs. 3. Acute liver failure. P&T later discounted gati as cause.	2 : 1 fatal 1. Pt had transplant but died of MOF. Roxithromycin, clindamycin are confounders. 2. Hepatic encephalopathy. Very little info (from Spain).
CALLED HEPATITIS With ↑ bili reported Bili WNL No LFTs given	9 5 1 3	7 4 (called cholestatic in 2) 1 2
NON-ALCOHOLIC STEATOHEPATITIS	1	0
HAD JAUNDICE OR DARK URINE With ↑ bili reported	4 3	8 4
HEPATOTOXICITY NOS	5	2 (1 reported complete LFTs incl ↑ bili)
HEPATOMEGALY	1	1 (reported complete LFTs incl ↑ bili but was positive for mono)
↑ LFTs WITH GI or ILL-DEFINED SYMPTOMS	0	2

Cases with biopsy showing necrosis:

Gatifloxacin: 2 definite, 1 a possibility (mentioned in company report but not info from reporter)

Moxifloxacin: 1

Other findings on biopsy:

Gatifloxacin: 1 case had eosinophilic hepatitis

Moxifloxacin: 1 case had periportal granulomas

Both of the two moxifloxacin liver failure cases were from foreign countries and lacked important information. At Dr. Meyerhoff's request, OPDRA contacted Bayer several times to try to get more information on the case involving a liver transplant; however, to date not enough information has been received from the company to assess the case adequately.

Because the Avelox® labeling does not address hepatocellular events, two of the more compelling hepatitis cases are presented below.

¹⁹ Since the searches were performed for the April analysis (close to the "data-lock" date for this document), five additional cases have been reported for gatifloxacin. One was a report of hepatitis; the four other cases appear to be cases of cholestatic or mixed hepatocellular/cholestatic hepatitis. In one of those cases, the patient had received Augmentin® (labeled for causing cholestatic and hepatocellular liver dysfunction) just prior to gatifloxacin, and no liver tests had been performed in the interim.

Two new cases have been received for moxifloxacin. One was a case of cholestatic hepatitis followed by erythema multiforme; the patient had earlier been treated with cefuroxime, which is labeled for causing both events. The other case was reported as hepatitis but included alkaline phosphatase levels 5xNL and increased bilirubin as well.

AERS # 3595281, Direct report, AZ.

A 43-year-old female patient presented to the ER with complaints of nausea, vomiting, and decreased appetite. She was jaundiced, and her labs were: AST 1360, ALT 2600, tbili 7.9, dbili 5.6, alk phos 150, albumin 3.9. She gave a history of having been treated with moxifloxacin approximately one month prior; the report does not list any other relevant history or concomitant medications. Abdominal ultrasound was negative for gallstones. HepA IgM, HepB core IgM, HepB surface Ag, and HepC IgG were all negative. The report states that since other etiologies for jaundice were ruled out, moxifloxacin was presumed to be the cause.

AERS # 3482285, Mfr # 200000644BWH, FL.

A 60-year-old male with COPD was treated with moxifloxacin for bronchitis. It was his only new medication. After three or four days he became nauseated and stopped the drug on his own. A few days later, however, he became jaundiced and returned to his physician. His AST was 51, ALT 432, alk phos 171, and tbili 18.1. He was sent to a gastroenterologist for a complete workup, but no other reason for the hepatitis could be found. The report states specifically that viral tests were negative as were ANA and alpha1-antitrypsin. When OPDRA contacted the patient's physician approximately six weeks after the event, all liver function tests had returned to normal.

As with the gatifloxacin hepatitis cases (and not surprisingly), these patients did not have baseline liver function tests. However, there is a temporal association of hepatitis with their use of moxifloxacin, no other medications are likely to have been the cause, and viral etiologies were ruled out.

2. PANCREATITIS:

The labeling for both Avelox® and Tequin® lists increased amylase as having occurred in clinical trials. Neither lipase changes nor pancreatitis per se are mentioned in either drug's labeling.

Moxifloxacin:

As of April 13, 2001, AERS contained five unduplicated reports of pancreatitis, and a case of increased amylase and lipase, associated with moxifloxacin. Two of the pancreatitis cases had been reported very briefly to a Bayer sales representative by one physician; when the FDA attempted to contact him for additional information, his office staff relayed a message stating that it had been determined that neither patient had had pancreatitis.

The three definite cases of pancreatitis are presented below. The reporter for the U.S. case was contacted and provided the Agency the hospital discharge summary.

AERS # 3424928, Mfr # 200000159BWH, —

A 48-year-old female of Japanese descent was hospitalized with severe abdominal pain two days after completing a five-day course of moxifloxacin for bronchitis. She was stated to be obese, with mild hypertension treated with atenolol (her only concomitant medication), but otherwise in good health and not previously hyperlipidemic. She denied any alcohol intake. On admission her serum amylase was 1159 and her triglycerides were 5320. Abdominal CT was compatible with pancreatitis with peripancreatic inflammation; mild ascites, an ovarian cyst, and mild atelectasis/pulmonary infiltration were also identified. She was made NPO and treated with iv fluids and later TPN. Numerous complications ensued (electrolyte abnormalities, UTI, anuria thought to be secondary to obstruction from ascites, wheezing); however, she was discharged two weeks after admission on no medications. Approximately one month later her triglycerides were 180 mg/dl (WNL).

AERS # 3426166, Mfr # 20005004BVD, —

A 54-year-old female with a history of gastritis, hyperlipoproteinemia, hepatic steatosis, alcohol abuse and pancreatitis reported developing spastic myalgia followed by various gastrointestinal disorders within a day of completing a five-day course of moxifloxacin for bronchitis. Three days later a radiologist found an enlarged right kidney suggestive of hydronephrosis, and fluid in the left upper quadrant which was interpreted as subileus. A CT scan performed 12 days later revealed pancreatitis with extensive exudation into the right pelvis; the report states that the pancreatitis was thought to be alcohol-induced. Numerous lab test results were given, including a peak amylase of 110 U/L (reference values not given, but this level would normally be considered WNL), lipase 254 U/L, triglycerides 522 mg/dl.

AERS # 3624654, Mfr # 200110429BVD, —

A 17-year-old female received roxithromycin for one week for sinusitis, followed a week later by ampicillin/sulbactam for 12 days. Thirteen days after that treatment ended, she received a four-day course of moxifloxacin. Four days after that she developed acute pancreatitis and was hospitalized with an amylase of 990 U/L and a lipase of 3312 U/L. The only other information given in the report is some additional admission lab results, of which the only abnormal findings were indirect bilirubin 2.3 mg/dl, LDH 137 U/L, and 7.8% lymphocytes in the urine.

Gatifloxacin:

As of April 13, 2001, AERS contained two unduplicated cases of pancreatitis and one of an asymptomatic increase in lipase and amylase associated with gatifloxacin. The reporters for both cases of pancreatitis were contacted. Although one agreed to send the FDA more information on the very scantily reported case, he has not done so. The reporter for the other case faxed voluminous information, which is presented briefly below.

AERS # 3458992, Direct report, _____, 2000.

A 71-year-old female, stated to be healthy except for hypertension, took gatifloxacin for six days for sinusitis. Her only other medications (all long-standing) were hydrochlorothiazide, metoprolol, and fosinopril. She did not use alcohol. She developed severe pancreatitis, nonketotic hyperosmolar hyperglycemic coma, acute renal failure, respiratory failure, and lactic acidosis. Her labs on hospitalization were: amylase 795, lipase 10596, creatinine 4.9, glucose 1379. A CT scan showed pancreatitis. She was discharged two weeks after admission, on insulin + glipizide for new-onset diabetes. The reporter stated that gallstones had been ruled out as the possible cause of her pancreatitis. He attributed all the events to the patient's pancreatitis which he thought was most likely due to gatifloxacin; however, additional cases of nonketotic hyperosmolar hyperglycemic coma unassociated with pancreatitis have been reported in association with the use of gatifloxacin (see *Cases of new-onset diabetes and profound hyperglycemic events* on pp.28-29).

3. GASTROINTESTINAL BLEEDING:

AERS contained 19 unduplicated cases of GI bleeding associated with moxifloxacin, and five cases associated with gatifloxacin. The events were serious (by regulatory definition) in 12 of the moxifloxacin cases; two patients died, one case was considered life-threatening, and nine patients were hospitalized. Two of the gatifloxacin cases were serious; one of the patients died and one was hospitalized.

Although three patients died as a result of their GI bleeds, the relationship to the fluoroquinolone appeared to be unlikely in the first case and was unclear in the other two. The first patient (AERS # 3603164) had been switched from moxifloxacin to vancomycin, ofloxacin, cloxacillin, and netilmicin 16 days before developing the GI bleed. In the second case (AERS # 3437921), the patient developed *C. difficile* (toxin found in stool) diarrhea while on moxifloxacin. The drug was discontinued, she experienced an improvement of symptoms, and *C. difficile* toxin was no longer detectable in stool. Moxifloxacin was not resumed, but 19 days later she developed *C. difficile* diarrhea again; the report states that it was not possible to determine if this was a relapse or a new episode. The patient developed a GI bleed followed by arrhythmia and death. No autopsy was performed, so the differential diagnosis for the etiology of the bleed was *C. difficile* colitis or stress ulcers. The third case (AERS # 3504305) was reported by multiple reporters and the details varied among the reports. Apparently, however, the patient had been taking ibuprofen, tramadol, and possibly celecoxib since an accident several months earlier. She developed abdominal symptoms with nausea and was given metoclopramide. At about the same time she was prescribed 10 days of gatifloxacin for a UTI, or possibly for "flu symptoms". Approximately 10 days later she was hospitalized with a history of vomiting bright red blood, and she died within two days. Autopsy showed that the cause of death was massive GI hemorrhage secondary to multiple ulcers of the stomach and large and small intestine.

Five additional moxifloxacin cases and two gatifloxacin cases were confounded because of concomitant medications known to cause such events, or because too little information was given to make an assessment (three of these cases were presented above under **DRUG-DRUG INTERACTIONS: Coumarin anticoagulants** on pp.9-10).

The twelve remaining moxifloxacin cases and two gatifloxacin cases all reported bloody diarrhea (or watery diarrhea with some blood) temporally associated with administration of the quinolone. *Clostridium difficile* toxin was found in one case, but stool cultures were negative for *Clostridium* in three cases. A report for one of the gatifloxacin cases states that stool was cultured and no enteric pathogens were isolated; it lists "*Salmonella*, *Shigella*, *Yersinia*, *Campy*, *Vibrio*, *E. coli* O157, *Aero* & *Plesio*, etc." but not *Clostridium*. Endoscopic/histologic examinations were

performed in six other cases and showed pseudomembranous colitis in two. The four other diagnoses were: proctitis in two, bleeding hemorrhoids, and "mild, nonulcerative colitis".

The **WARNINGS** section of the labeling for all fluoroquinolones contains several paragraphs on pseudomembranous colitis or "antibiotic-associated colitis" associated with antibacterial agents. It does not mention bloody diarrhea but does indicate that the severity may range from mild to life-threatening. Most of these cases appear to have resulted from pseudomembranous colitis and thus would not be considered unexpected for either drug.

D. HEMATOLOGIC:

Moxifloxacin:

The current Avelox® labeling lists the following hematologic events as adverse reactions seen in clinical trials: eosinophilia, leukopenia, thrombocytopenia, and thrombocytopenia. It also lists the following laboratory changes seen in clinical trials: increased MCH, neutrophils, and WBCs; and decreased basophils, eosinophils, hemoglobin, neutrophils, and RBCs.

AERS was searched for any moxifloxacin case coded with a term under the BLOOD & LYMPHATIC SYSTEM DISORDERS System-Organ-Class or with the term COOMBS DIRECT TEST POSITIVE; the search would not have captured cases coded with terms indicative of asymptomatic abnormal blood cell counts.

Of the 13 unduplicated cases retrieved, two were reports of unspecified anemia and one was a report of asymptomatic leukopenia; these three cases appear to be adequately covered by the current labeling.

There were four cases of deficiencies in more than one blood cell line, but they were unassessable from the information available to date.

The first (AERS #3426166) was a German report of "blood dyscrasia" with multiple lab test results provided. The patient's platelets had indeed fallen from pretherapy 220,000 to 19,000 after treatment with moxifloxacin, and demonstrated a gradual postdiscontinuation rise back to normal levels one month later. However, her RBCs were actually below normal before therapy and had risen after moxifloxacin treatment, although they then fell again. Her WBCs were never low.

The second case (AERS #3470233) was a German report of deficiencies in all three blood cell lines along with a painful, enlarged spleen. Followup states that the patient was later diagnosed with paroxysmal nocturnal hemoglobinuria. The laboratory results provided all have dates prior to the use of moxifloxacin.

The third case (AERS #3498176) was a German report of syncope with nausea and vomiting occurring two hours after the first intake of moxifloxacin. Blood tests at that time showed decreased RBCs, platelets, and coagulation; the patient had just completed a course of tetracycline.

The final case (AERS # 3601168) was a very poorly documented U.S. report of pancytopenia resulting in hospitalization. OPDRA attempted to contact the reporter without success, and no followup information has been received from Bayer.

There was also an extremely confusing Spanish report (AERS # 3591057) of agranulocytosis in which the patient later died of renal failure thought secondary to sepsis. The laboratory values provided indicate that the patient's WBC was low (2.9) even prior to the administration of moxifloxacin.

Three of the five remaining cases were reports of thrombocytopenia resulting in petechiae, purpura, and/or bleeding. One was a U.S. report of thrombocytopenic purpura with few other details provided. Two German cases were better documented and are presented briefly below.

AERS # 3435320, Mfr # 1199910637, —

A 58-year-old female whose only concomitant medications were estrogen and l-thyroxine was treated with moxifloxacin for 11 days for pneumonia. The next day she developed petechiae on her legs and hemorrhage of the oral mucosa and was hospitalized. Her platelet count was 5000 and a Rumpel-Leede test was positive. A bone marrow biopsy showed increased megakaryocytes but was otherwise normal. Her platelet count had risen to 122,000 without therapy by discharge three days later and was stated to have normalized two days after that.

AERS # 3467510, Mfr # 1200004344, —

A 70-year-old male who had had a platelet count of 180,000 four months prior was treated with moxifloxacin for six days for bronchitis. During treatment, he complained about pain in his limbs. Two days after therapy ended he noticed petechiae on his arms and legs, and later that day developed epistaxis. He was hospitalized; a platelet count apparently obtained five days later was 1000. A bone marrow biopsy showed "reactive bone marrow changes without any hint at a disorder of thrombopoiesis". He was treated with prednisolone and his platelet count increased within three days. The next value provided (209,000) was apparently obtained about three weeks later. The report stated that prednisolone was then discontinued and the platelet count fell again to 95,000 within the next two weeks. The cause of the patient's thrombocytopenia was thought to be either his underlying infection or the moxifloxacin.

The two final cases were fairly well-documented U.S. reports of hemolytic anemia in young, healthy patients.

AERS # 3509329, Mfr # 200001781BWH, —

A 20-year-old, 360-lb male with a history of penicillin allergy was treated with moxifloxacin for six days for sinusitis (symptoms: weakness, fatigue, dizziness). His only concomitant medications were loratadine and Midrin®. About four days after starting moxifloxacin he developed jaundice. The day after treatment ended he went to the ER complaining of increasing shortness of breath and weakness, low-grade fever with no chills, appetite reduction, jaundice, and dark urine. His hemoglobin was 3.9 and his hematocrit was 11.3 with an LDH of 4615 and a bilirubin of 7.2. A hematologist was consulted and agreed with the diagnosis of acute hemolytic anemia, probably drug-induced. A Coombs' test was later found to be positive. The patient was given a blood transfusion and started on steroids; within two days his bilirubin began decreasing. At the time of discharge five days later, hemoglobin was 10, hematocrit 27.9, bilirubin 3.9, and LDH 3228.

AERS # 3556439, Mfr # 200002289BWH, —

A 43-year-old female with hypertension and hypothyroidism, receiving l-thyroxine, hydrochlorothiazide, fosinopril, and lansoprazole, was given moxifloxacin for bronchitis. The next day she contacted her physician with complaints of heart racing and shortness of breath. The following two days she again reported those symptoms so she was told to go to the ER on the third day. Her hemoglobin was 5.5, her hematocrit was 17.0, and unconjugated bilirubin was 3.4. She was admitted with a diagnosis of hemolytic anemia and was given steroids and two units of packed RBCs.

Gatifloxacin:

The current Tequin® labeling lists ecchymosis and epistaxis as adverse reactions seen in clinical trials. It also lists neutropenia as a laboratory change seen in clinical trials.

AERS was searched using the same criteria as had been used for moxifloxacin. Of the 17 unduplicated cases retrieved, there was one report each of "bone marrow toxicity" (OPDRA attempts at followup were unsuccessful), normocytic anemia, decreased RBCs, and disseminated intravascular coagulation (following hepatitis and renal failure).

There were five reports of deficiency involving more than two cell lines. However, in two cases of anemia with thrombocytopenia, those events were discovered coincidentally on admission when the patients were hospitalized for hepatorenal syndrome/sepsis and muscle spasms, respectively. A case of pancytopenia from Brazil (AERS # 3609842) involved an AIDS patient whose platelet and hemoglobin levels were low prior to the use of gatifloxacin (no baseline WBC was given on the report). Another indication that he had a hematologic disorder prior to the use of gatifloxacin is that he had a bone marrow biopsy two days after starting the drug, even though no blood cell levels had been obtained since starting therapy.

The two other cases were somewhat more compelling and are presented below.

AERS # 3578031, Mfr # 10622587, —

A 34-year-old female with a history of allergy to sulfas was given clarithromycin for three weeks for sinusitis. When that treatment was unsuccessful, she was switched to gatifloxacin. She was also receiving cetirizine and ibuprofen (dates not stated). On day 11 of gatifloxacin therapy, she developed a severe fever, myalgia, and swollen lymph nodes but a CBC that day showed minimal changes: WBC 5.0; RBC 4.32; PLT 59,000. However, two days later all drugs were discontinued when a CBC showed "significant pancytopenia": WBC 2.0; RBC 3.80; PLT 100,000 (the latter two values are listed in the lab section as WNL). The following day the patient's fever resolved and she felt better although her WBC had fallen further to 1.9 (RBC had increased to 4.16 and PLT to 124,000). Two days later "laboratory tests began to normalize" (no results provided). Her physician felt it was a "toxic drug reaction to Tequin".

AERS # 3586778, Mfr # 10613529, —

A 94-year-old female with a history of idiopathic thrombocytopenic purpura treated by splenectomy received gatifloxacin for pneumonia. Treatment was stopped after 15 days because the patient presented with rectal bleeding and was discovered to have a platelet count of 5000 and a hemoglobin of 8.8. Labs obtained the day gatifloxacin was started had shown a platelet count of 195,000 and hemoglobin of 11. The patient was hospitalized and treated with platelets and PRBCs.

The eight remaining cases all involved thrombocytopenia, with petechiae, purpura and/or bruising in two of the cases. Those two cases are presented below. Two of the six remaining cases were poorly reported, and OPDRA attempted followup without success. In another case famotidine (labeled for rarely causing thrombocytopenia) was given on the same dates as gatifloxacin and was also considered suspect. Two other cases were primarily reports of other events (rhabdomyolysis, nonketotic hyperosmolar hyperglycemia). The sixth case, however, was interesting because of a positive rechallenge with another fluoroquinolone, so it is also presented below.

AERS # 3475549, Mfr # 10321826, —

A 38-year-old female, on fluoxetine (labeled for rarely causing thrombocytopenia, petechiae, and purpura) for five years, was enrolled in a clinical trial of gatifloxacin for upper respiratory infections. Four days after starting gatifloxacin, she developed petechiae and purpura. She stopped the drug on her own the next day; the following day her platelet count was 2,000 and she was hospitalized. She received a platelet transfusion but it had no effect on her platelet level. Followup reports indicated that the patient was given gamma-globulin and prednisone and was continued on gatifloxacin during her hospital stay, completing 14 doses. She was discharged with a normal platelet count (211,000) the day her gatifloxacin treatment ended. Following discharge, she was given dexamethasone on a tapering schedule and her platelet count remained fairly stable. The hematologist on the case suspected a viral etiology. At one point an ANA was positive but a rheumatologist was consulted and repeat serologic testing was negative for connective tissue disorders and lupus. The patient did disclose a family history of hemophilia and admitted to "a drink of quinine" the day before she was hospitalized.

AERS # 3592629, Mfr # 10664811, —

A 97-year-old female on captopril and furosemide was hospitalized after a fall. She received a flu vaccination and cefuroxime, followed by iv gatifloxacin, for CAP. Eight days after starting gatifloxacin, she experienced severe generalized bruising; her platelet count was 24,000. Gatifloxacin was stopped and she was given a platelet transfusion. Her platelet counts the next three days were: 84,000; 114,000; and 115,000. However, she developed congestive heart failure and expired six days after gatifloxacin was discontinued.

AERS # 3623461, Direct report, —

An 83-year-old female with allergies to penicillin, sulfa, and codeine was admitted for a gangrenous bowel and had a total colectomy and splenectomy. She received iv gatifloxacin for five days. Her platelet count was 210,000 the day gatifloxacin was started but had dropped to 58,300 the following day. Gatifloxacin was continued for four more days, at which time her platelet count was 15,000. After discontinuing the drug, her platelets climbed to 53,000 and 74,000 over the next two days. It was then decided to treat her with iv levofloxacin. The following day her platelets had dropped again to 39,000 and levofloxacin was also discontinued.

These cases are less compelling than those reported for moxifloxacin; however, fluoroquinolones as a class are known to cause thrombocytopenia and there is a temporal relationship with gatifloxacin in some of the cases above.

E. METABOLIC/ENDOCRINE:

1. GLUCOSE ABNORMALITIES:

Since approval, the **PRECAUTIONS** section of the Tequin® labeling has contained a paragraph similar to some of the other fluoroquinolones; it states that both hyper- and hypoglycemia have been reported, usually in diabetic patients receiving hypoglycemic agents. In addition, the **ADVERSE REACTIONS** section of the Tequin® labeling states that both events as well as diabetes mellitus occurred in clinical trials. The Avelox® labeling does not contain a statement in the **PRECAUTIONS** section; hyperglycemia (but not hypoglycemia) is listed under **ADVERSE REACTIONS** as having occurred in clinical trials.

In July 2000, OPDRA sent DSPIDP a document (PID D000497) summarizing all the cases of hyper- and hypoglycemia, including cases of nonketotic hyperglycemic-hyerosmolar coma, which had been reported to the FDA in association with the use of gatifloxacin. Bristol-Myers Squibb later filed a Changes Being Effected supplement slightly strengthening the existing sections relating to glucose abnormalities. OPDRA remains concerned, however, because the events reported with gatifloxacin seem to be more severe than those reported with other fluoroquinolones. Preliminary studies are being conducted under OPDRA's Cooperative Agreement program utilizing large claims databases; to date, however, there is not enough use of the newer products at the various sites to be able to compare incidence rates of such rare events.

Reporting rates:

In Tables 10 and 11, the gatifloxacin reporting rates for serious hypo- and hyperglycemia are compared with those for various other fluoroquinolones at different timeperiods after approval. Moxifloxacin is highlighted as well since it is also the subject of this document.

TABLE 10: U.S. REPORTING RATE FOR SERIOUS²⁰ GLUCOSE ABNORMALITIES DURING THE FIRST YEAR POSTMARKETING²¹ FOR SELECTED FLUOROQUINOLONES

DRUG	APPROVAL DATE	U.S. ORAL RX FIRST YEAR ²²	SERIOUS HYPO-GLYCEMIA FIRST YEAR ²³	ONE-YEAR HYPO-GLYCEMIA REPORTING RATE per Rx	SERIOUS HYPER-GLYCEMIA FIRST YEAR ²⁷	ONE-YEAR HYPER-GLYCEMIA REPORTING RATE per Rx
Ciprofloxacin	10/87	/	0	—	1	0.3
Gatifloxacin	12/99		14	7.8	8	4.4
Levofloxacin	12/96		0	—	1	0.7
Moxifloxacin	12/99		0	—	4	5.0
Ofloxacin	12/90		0	—	1	0.8
Temafloxacin ²⁴	1/92		33	165	4	20
Trovafoxacin	12/97		5	4.1	1	0.8

²⁰ Resulting in death, considered life-threatening, or involving hospitalization or disability. Negates differences caused by Bristol-Myers Squibb's waiver allowing nonreporting of nonserious labeled events (see p.4).

²¹ To attempt to eliminate differences caused by the so-called "new drug reporting phenomenon". Does not, however, address differences caused by increased reporting in general.

²² U.S. oral outpatient prescriptions from retail pharmacies. Data obtained from the IMS HEALTH, INC. NPA-Plus™ database; information is copyrighted and cannot be used outside the FDA without prior permission from IMS HEALTH, INC.

²³ AERS was searched for reports received through the 15th of the month following the one-year anniversary, to allow for a reporting lag. The numbers used in this comparison are raw, unevaluated counts and may include duplicate, literature, and study reports; causality has not been assessed. May also include cases in inpatients or patients treated with iv drug, so the numerators and denominators are not strictly comparable.

²⁴ Used as a comparator because the FDA had been concerned about hypoglycemia before the drug was withdrawn.

TABLE 11: U.S. REPORTING RATE FOR SERIOUS²⁵ GLUCOSE ABNORMALITIES THROUGH CALENDAR YEAR 2000 FOR SELECTED FLUOROQUINOLONES

DRUG	U.S. ORAL RX ²⁶ THROUGH 2000 in _____	SERIOUS HYPO- GLYCEMIA THROUGH 2000 ²⁷	HYPO- GLYCEMIA REPORTING RATE THROUGH 2000 _____ Rx	SERIOUS HYPER- GLYCEMIA THROUGH 2000 ³¹	HYPER- GLYCEMIA REPORTING RATE THROUGH 2000 _____ Rx
Ciprofloxacin		23	0.2	7	0.06
Gatifloxacin		14	7.8	8	4.4
Levofloxacin		11	0.5	6	0.3
Moxifloxacin		0		4	5.0
Ofloxacin		10	0.5	6	0.3
Trovafloxacin		11	4.8	8	3.5

Since glucose abnormalities would be more likely in diabetic patients, the IMS HEALTH, INC. National Disease and Therapeutic Index™ database was queried for three of the newer fluoroquinolones (gatifloxacin, levofloxacin, and moxifloxacin) regarding the diabetic status of the patients treated²⁸. For calendar year 2000, the percentage of patients receiving the three drugs for respiratory infections in whom diabetes was listed as a concomitant condition was approximately the same (1.9, 2, and 1%, respectively).

Gatifloxacin/moxifloxacin comparison:

All AERS reports of decreased or increased blood glucose levels with moxifloxacin or gatifloxacin as a suspect drug²⁹ were obtained for hands-on analysis.

TABLE 12: GATIFLOXACIN- AND MOXIFLOXACIN-ASSOCIATED HYPOGLYCEMIA

EVENT	GATIFLOXACIN	MOXIFLOXACIN
Unduplicated cases	N=46	N=4³⁰
Age	N=36	N=3
Range	32-96	46-65
Median	74	48
Mean	72.6	53
Gender	N=36	N=3
Male	8	2
Female	28	1
Serious	N=33	N=0
Life-threatening	5	—
Hospitalization	28	—
Time to onset (days)	N=30	N=3
Range	<1-3.5	<1
Median	1	<1

²⁵Resulting in death, considered life-threatening, or involving hospitalization or disability. Negates differences caused by Bristol-Myers Squibb's waiver allowing nonreporting of nonserious labeled events (see p.4).

²⁶ U.S. oral prescriptions from retail pharmacies. Data obtained from the IMS HEALTH, INC. NPA-Plus™ database; information is copyrighted and cannot be used outside the FDA without prior permission from IMS HEALTH, INC.

²⁷ The numbers used in this comparison are raw, unevaluated counts and may include duplicate, literature, and study reports; causality has not been assessed. May also include cases in inpatients or patients treated with iv drug, so the numerators and denominators are not strictly comparable.

²⁸ Information from IMS HEALTH, INC. is copyrighted and cannot be used outside the FDA without prior permission from IMS HEALTH, INC.

²⁹ Additional reports of these events with nonserious outcomes have been listed in the Tequin® periodic reports but were not submitted to AERS because of Bristol-Myers Squibb's waiver (see p.4): Bayer does not have a waiver for Avelox® so all moxifloxacin reports should have been submitted to AERS.

³⁰ There is an additional report describing a woman who was treated with moxifloxacin for five days around the time of conception; her newborn infant experienced episodes of hypoglycemia during the first 30 hours of life.

EVENT	GATIFLOXACIN	MOXIFLOXACIN
Time to onset (days), cont'd.		
Mean	1.4	<1
Lowest blood glucose	N=28	N=4
Range	20-79	43-“<60”
Median	37	50
Mean	39	51
Baseline blood glucose	N=6	N=0
Range	65-156	---
Median	112.2	---
Mean	115	---
History of diabetes	N=42	N=2
No history of diabetes	N=2	N=1
Symptomatic	N=18	N=1
Adrenergic symptoms ³¹	N=6	N=0
CNS symptoms ³³	N=12	N=0

TABLE 13: GATIFLOXACIN- AND MOXIFLOXACIN-ASSOCIATED HYPERGLYCEMIA

EVENT	GATIFLOXACIN	MOXIFLOXACIN
Unduplicated cases	N=45	N=9
Age	N=38	N=8
Range	27-87	20-75
Median	68.5	49
Mean	64.2	49.5
Gender	N=41	N=9
Male	N=17	N=3
Female	N=24	N=6
Serious	N=20	N=6
Death	N=1	N=0
Life-threatening	N=3	N=2
Hospitalization	N=16	N=4
Time to onset (days)	N=32	N=9
Range	<1-39	<1-8
Median	5	2
Mean	6.5	3
Highest blood glucose	N=34	N=8
Range	122-1712	129-275
Median	493	178
Mean	573.5	190
Baseline blood glucose	N=15	N=0
Range	92.5-433	---
Median	126	---
Mean	150.8	---
History of diabetes	N=24	N=1
No history of diabetes	N=9	N=1
Events	N=14	N=2
Weakness, headache, or mental changes	N=6	N=1
Hyperosmolar nonketosis	N=4	N=0
New-onset diabetes	N=3	N=0

³¹ Berkow R, Fletcher AJ, eds. The Merck manual of diagnosis and therapy. 16th ed. Rahway, NJ: Merck & Co., Inc. 1992;1129.

Aside from being fewer in number, the moxifloxacin cases were quite different from the gatifloxacin cases in a number of ways. They were less severe, indicated not only by the percentage categorized as serious but also by the degree of glucose depression or elevation as well as the number of patients stated to be symptomatic. In addition, for both types of events there was a lower percentage of patients stated to have a history of diabetes. Also, only two of the moxifloxacin hyperglycemia cases were actually submitted as reports of hyperglycemia; in the remaining eight cases, patients were hospitalized for other events and hyperglycemia was found on admission.

Among the gatifloxacin cases themselves, there was a definite difference between the cases of hyper- and hypoglycemia, raising the possibility of a different mechanism of action. The overwhelming majority of the hypoglycemia patients had a history of diabetes (42 of the 44 for which that information was provided, or >95%); among the hyperglycemia cases, only 24 of 33, or <73%) had a history of diabetes. In addition, the time to onset was very short for hypoglycemia but was more protracted in the cases of hyperglycemia; even after excluding the 39-day onset as an outlier, the median was still 5 days and the mean had decreased only slightly to 5.5 days.

Cases of new-onset diabetes and profound hyperglycemic events:

Because a number of reports of new-onset diabetes and profound hyperglycemic events such as hyperglycemic-hyperosmolar nonketotic coma had been reported in association with gatifloxacin, AERS was searched for all reports of such events with any fluoroquinolone and the cases were obtained for hands-on analysis.

TABLE 14: NEW-ONSET DIABETES AND PROFOUND HYPERGLYCEMIC EVENTS REPORTED FOR THE FLUOROQUINOLONES

DRUG	EVENT ²²	UNDUPLICATED CASES IN AERS
Ciprofloxacin	New-onset diabetes	1
Enoxacin	---	0
Gatifloxacin	Nonketotic hyperglycaemic-hyperosmolar coma	3
	Diabetic hyperosmolar non ketoacidosis	1
	New-onset diabetes	3
Grepafloxacin	---	0
Levofloxacin	Diabetic ketoacidosis	1
	New-onset diabetes	2
Lomefloxacin	New-onset diabetes	1
Moxifloxacin	---	0
Norfloxacin	Diabetic coma	1
	New-onset diabetes	1
Ofloxacin	New-onset diabetes	7
Sparfloxacin	---	0
Trovafoxacin/ alatrofloxacin	Diabetic coma	1
	Diabetic ketoacidosis	1
	New-onset diabetes	4

²² AERS was searched for all cases coded with any of the following terms: DIABETES MELLITUS NOS, DIABETIC COMA NOS, DIABETIC HYPEROSMOLAR NON KETOACIDOSIS, DIABETIC KETOACIDOSIS, NONKETOTIC HYPERGLYCAEMIC-HYPEROSMOLAR COMA.

As can be seen from Table 14, fluoroquinolones other than gatifloxacin have also been associated with new-onset diabetes. The characteristics of the cases reported with gatifloxacin appeared similar to those reported with the other drugs. Some of the cases were confounded by other suspect medications (especially steroids with the other drugs), and some of the reports had been received from consumers with no confirmation by health professionals. Three of the trovafloxacin cases and one of the gatifloxacin cases were reported to have occurred at time periods ranging from two months to three years after the "suspect" drug had been discontinued.

Apart from new-onset diabetes, gatifloxacin had four unduplicated reports of nonketotic hyperglycemic-hyperosmolar events³³. One of the patients had a history of diabetes, but the three other patients were specifically stated not to have such a history. The patients ranged in age from 53 to 71 years; all were female. Weight was listed on only two reports; one patient weighed 122 lb, while the other weighed 185 lb. No baseline blood glucose was provided for one of the cases, and in another the patient's physician stated only that it had been "normal" about a year earlier. In the two other cases, baseline glucose was 117 and 173, respectively (the second case was the diabetic patient, who was stated to have been "fairly-well" controlled at about that level). Time to onset ranged from 2.5 to 12 days after starting gatifloxacin. There were no other new drugs in any of the cases. Glucose levels at the time of the event ranged 950 to 1712. Three of the patients became comatose. One of the cases is presented below; an additional case was presented under **PANCREATITIS** on p.21.

AERS # 3467268, Mfr 10359396, [REDACTED]

A 65-year-old female with ischemic heart disease and congestive heart failure but no history of diabetes had been hospitalized with gram-negative pneumonia and had received gatifloxacin iv; her blood glucose had apparently been between 115 and 120 at that time. On discharge she was placed on oral gatifloxacin. Two to three days later she was found on the floor, "unresponsive and confused". She was taken to the ER where her glucose was measured at 1712. (Her physician stated that he had never seen a blood glucose that high in 25 years of practice.) She was admitted and treated for nonketotic hyperosmolar coma. The physician also reported two other cases of extremely high glucose levels temporally associated with gatifloxacin and recovering quickly once the drug was discontinued; one was one of the other cases reported as nonketotic hyperosmolar coma (glucose 950) while the other was reported only as hyperglycemia (glucose approximately 600, with headache and dizziness).

Among the other fluoroquinolones, there was only one report of a possibly similar event: hyperglycemic coma associated with norfloxacin. An 84-year-old female with a history of type II diabetes was hospitalized in a coma the day after completing a 10-day course of norfloxacin for UTI. She had no other new drugs. Her blood glucose was 843 mg/dl.

There was also one report each of diabetic ketoacidosis with levofloxacin and trovafloxacin, and "near-diabetic coma" with trovafloxacin. The patient in the levofloxacin case was receiving cyclosporine following a renal transplant, and it was thought that levofloxacin had interacted with the cyclosporine causing cyclosporine toxicity resulting in diabetic ketoacidosis. The two Trovan® cases were poorly documented. One of the patients had AIDS, but the report did not list any concomitant medications; protease inhibitors would be a confounding factor if the patient was on any of them. The ketoacidosis in the other case did not occur until eight days after trovafloxacin had been discontinued. The patient had received prochlorperazine (labeled for causing hyperglycemia) in the interim.

2. HYPOKALEMIA:

The Tequin® labeling states that unspecified "electrolytes abnormalities" occurred during clinical trials of gatifloxacin. The Avelox® labeling lists increases in ionized calcium and chloride during clinical trials. The "AERS all adverse events printout" for moxifloxacin showed nine cases coded as hypokalemia and two coded as decreased blood potassium. Although the gatifloxacin printout

³³ After the "data-lock date" for this document, the FDA received reports from a physician of four cases of hyperglycemia, in two of which blood sugar levels were over 1000 and the patients died. The cases are currently being actively investigated by Bristol-Myers Squibb.

only showed a total of four cases coded as either of those events, the cases for both drugs were ordered for hands-on analysis.

After eliminating duplicate cases, there were nine cases associated with moxifloxacin and three with gatifloxacin. However, in four of the moxifloxacin cases and one of the gatifloxacin cases, the abnormal potassium was not reported as an adverse event but was just an incidental finding on admission. Three of the five remaining moxifloxacin cases were confounded by recently-introduced drugs (diuretics in two cases, methylprednisolone in the other) labeled for causing potassium loss; in one of those three cases, the diuretics were thought to be the cause of the hypokalemia.

There were thus only two cases associated with each drug in which hypokalemia was reported as an adverse event and no confounding medications were listed.

F. NEUROLOGIC:

CONVULSIONS:

The labeling for both Tequin® and Avelox® contains a paragraph under **WARNINGS** stating that convulsions have been reported in patients receiving quinolones. In addition, the **Information for Patients** section in the labeling for both drugs provides the same information and indicates that patients should notify their physicians if they have a history of seizures. However, the Avelox® labeling does not provide any indication that seizures or convulsions have been reported in association with moxifloxacin; the Tequin® labeling lists "convulsion" as having occurred in clinical trials of gatifloxacin.

AERS was searched for both drugs using the terms CONVULSIONS NOS, CONVULSIONS NOS AGGRAVATED, and GRAND MAL CONVULSION. Similar raw numbers of cases were found with both drugs: 42 with moxifloxacin and 40 with gatifloxacin³⁴.

Moxifloxacin:

After eliminating duplicate cases and cases in which followup indicated that no seizure or convulsion had occurred, there were 25 unduplicated cases. However, in one case it sounds unlikely that the event was a seizure ("patient acted spacey and then passed out") although it was reported as a possible seizure by the physician. One report from a consumer also sounds unlikely to have been a seizure; he experienced a "surge of current" and nausea 15 minutes after his first dose of moxifloxacin. In three patients with a history of seizures, subtherapeutic anticonvulsant levels were later found. Three other cases were poorly documented and did not provide enough information to make an assessment of the possible role of moxifloxacin.

The 17 final cases, however, were suggestive of a possible moxifloxacin neurotoxic effect leading to seizures, although only five indicated that any sort of neurologic workup had been performed and only two of the seizures were stated to have been observed by health professionals. (Five of the reports were from consumers.) The events were stated to be temporally related to the use of moxifloxacin in 16 of the cases, with a time to onset ranging from less than 24 hours to six days in 15 cases and "during treatment" in the 16th. Eight reports indicated that the events resolved when moxifloxacin was discontinued. Age was given in all but two reports, and only three of the patients were elderly (one was 66 and two were 83 years old); all of the others were 52 years of age or less. Only two had histories of cardiovascular disorders. Two were stated to be on no other medications, and only four were on any other new medications. In three of the four, the

³⁴ In addition, the Tequin® periodic reports were reviewed to see if any cases had not been submitted to AERS because of the Bristol-Myers Squibb waiver (see p.4); all cases had been submitted because they were serious by regulatory definition.

other new drug is not labeled for causing seizures. In the fourth (the only case potentially confounded by a concomitant drug), the patient's previous anticonvulsants had reportedly caused side effects and she had been switched to phenobarbital some time in the month before moxifloxacin was started.

Eight (possibly nine) of the patients had risk factors for quinolone-induced seizures as listed in the labeling: a history of seizures in seven, and NSAID use in one (possibly two). An additional patient had a history of migraines and one was stated to drink three bottles of vodka per week.

One of the cases is presented below.

AERS # 3450882, Mfr # 200000631BWH, —

A 31-year-old male "athletic" patient, stated to have a negative medical history but also on fluticasone (his only concomitant medication), was treated with moxifloxacin for ten days for pneumonia. During treatment, he experienced a grand mal seizure while at work and was told to discontinue moxifloxacin. Followup information sent in more than one month later said that the patient had experienced no further seizures after moxifloxacin was discontinued.

Gatifloxacin:

Dr. Ekopimo Ibia, the new medical officer for gatifloxacin, suggested a hands-on review of the gatifloxacin cases to put the moxifloxacin cases in context (since convulsions are listed in the Tequin® labeling). The case report forms were therefore obtained; however, because the event is labeled, most of the cases came in as periodic reports and included very little documentation. Although only three of the moxifloxacin cases were considered too poorly documented to assess, 16 of the 40 gatifloxacin cases provided no information other than the fact that a patient on the drug had experienced a seizure or convulsion. Another four cases included the time to onset but no other information, and a fifth case stated that the patient had Down's syndrome but gave no other information.

Of the 19 other cases, six were excluded from this analysis. Three were duplicate cases. Another case was primarily a report of exacerbated renal and heart failure which were followed by "a hypoxic event with associated seizure". One was a consumer report of "excruciating pain throughout her whole body", subsequent vomiting, and "convulsions for about three hours". In another case the patient's theophylline level was found to be 33.6 mg/L.

The 13 remaining cases were evaluated against the 17 moxifloxacin cases. Six patients had neurologic workups. Only one of the seizures was stated to have been observed by a health professional (two of the reports were from consumers). The events were stated to be temporally related to the use of gatifloxacin in 12 of the cases, with a time to onset ranging from "after the first dose" to seven days. Four reports indicated that the events resolved after gatifloxacin was discontinued. Age was given in all but one report and only two of the patients were elderly; all of the others were 55 years of age or less. Only one had a history of a cardiovascular disorder (hypertension). Two patients were stated to be on no other medications, and only one was on any other new medication (ibuprofen).

Four of the patients had risk factors for quinolone-induced seizures as listed in the labeling: a history of seizures in one, and NSAID use in three. Another patient had Alzheimer's disease. Two other patients were on bupropion, which contains **WARNINGS** about seizures in its labeling.

It thus appears that the evaluable cases reported for gatifloxacin (labeled for convulsions) are similar to those reported for moxifloxacin (not labeled for convulsions except in class labeling sections).

G. RENAL:

The current Avelox® labeling states that "abnormal kidney function" was seen in clinical trials. The current Tequin® labeling does not mention any renal effects.

A recent review article³⁵ summarized 44 published cases of renal failure associated with fluoroquinolones found in a search of MEDLINE. All but two of the cases were associated with ciprofloxacin. (The Cipro® labeling states that interstitial nephritis and renal failure per se were seen in clinical trials.) Although moxifloxacin and gatifloxacin were among the drugs covered in the review article, neither had been approved at the time the search was run.

AERS was searched for gatifloxacin and moxifloxacin using an OPDRA-defined group of terms which would capture any renal effect, including abnormal laboratory values such as increased BUN or creatinine. After eliminating duplicate cases, there were 33 cases reporting renal effects associated with gatifloxacin and 13 with moxifloxacin. The cases are summarized briefly below.

Moxifloxacin:

The 13 moxifloxacin cases were reported as follows:

Renal failure:	5
Hepatorenal syndrome:	1
Anuria:	1
Oliguria:	1
Uremia:	1
Renal insufficiency:	1
Increased BUN and/or creatinine:	3

Following hands-on review of the cases, there did not appear to be a signal at this time that moxifloxacin is nephrotoxic. Four of the cases were rather poorly documented, lacking information on either concomitant medications or relevant medical history; since they were foreign reports, followup is problematic.

Among the ten cases of clinical renal events, five were thought by the reporters to have resulted from other events (including some events which may have been caused by moxifloxacin): treatment of pulmonary edema; worsening of patient's underlying cirrhosis (the case of hepatorenal syndrome); right heart failure; hepatitis; sepsis. In a sixth case, the patient was hospitalized with hematuria and acute renal failure the day after starting moxifloxacin, and mesangioproliferative IgA nephritis was diagnosed on biopsy; however, the patient had had dark urine before starting the drug. Netilmycin was administered concomitantly with moxifloxacin in a seventh case, and too little information was given in the eighth case to make any assessment as to the etiology of the reported anuria.

The two remaining cases are presented briefly below.

AERS # 3547230, Mfr # 200002592BWH, [REDACTED]

A 60-year-old female with a history of multiple UTIs and a remote history of hepatitis A received moxifloxacin for nine days for a UTI. She was taking no other medications. Two weeks after completing therapy, she presented to the ER with oliguria and shortness of breath. She was found to have pleural effusions. Lab values were: BUN 37, creatinine 2.1, AST 161, ALT 154, alk phos 431, LDH 1229, Hct 33.7. All labs were stated to have been WNL four months earlier. When the patient's physician reported the case to Bayer (a month after submitting the data listed above to the FDA), he described it as a case of **acute renal failure** and liver toxicity.

AERS # 3573392, Mfr # 200090015BVD, [REDACTED]

A 66-year-old male with a history of dilated cardiomyopathy, COPD, hypertension, rheumatoid arthritis, and "compensated renal insufficiency" was treated with moxifloxacin for nine days for acute exacerbations of COPD. The report stated that the patient's creatinine had last been determined about six months prior and had been 1.2 mg/dl at that time. His only concomitant medications were chronic. On the last day of moxifloxacin therapy he was

³⁵ Lomaestro BM. Fluoroquinolone-induced renal failure. Drug Safety 2000;22:479-85.

hospitalized with severe dyspnea. **Acute renal failure** was diagnosed based on admission labs: creatinine 4.58 mg/dl and BUN 130 mg/dl. He was treated with triamterene and hydrochlorothiazide. His clinical course was complicated by "cardiac decompensation" which required treatment with catecholamines. On discharge three weeks after admission, his creatinine was 1.2 mg/dl and BUN was 40 mg/dl.

Of the three cases reporting only increased BUN and/or creatinine, one was a report of a patient who experienced a cardiac arrest and seizures while on moxifloxacin; the abnormal labs were among others discovered on hospitalization. Another patient developed *C. difficile* diarrhea and increased creatinine while taking moxifloxacin. The third case was more suggestive of an actual moxifloxacin effect on the kidney but was poorly documented; serum creatinine was stated to have gone from 0.8 mg/dl to 4.6 mg/dl during moxifloxacin therapy in a patient of unstated age and gender, on multiple chronic medications.

Gatifloxacin:

The 33 gatifloxacin cases were reported as follows:

Renal failure:	15
Interstitial nephritis:	1
Anuria:	1
Renal insufficiency/toxicity:	6
Decreased creatinine clearance:	2
Increased BUN and/or creatinine:	8

Seven of the 23 cases of clinical renal disorders were thought by the reporters to have resulted from other events (including events possibly caused by gatifloxacin): hyperosmolar hyperglycemic coma (two cases; see *Cases of new-onset diabetes and profound hyperglycemic events* on pp.28-29); dehydration (two cases); sepsis; hepatitis; rhabdomyolysis. In 13 additional cases, too little information was reported to make an assessment of the role of gatifloxacin; OPDRA has attempted to obtain additional information on most of the poorly documented cases but has only been successful in five instances.

Two of the three remaining cases are presented briefly below. All were reports of renal failure temporally associated with gatifloxacin therapy in elderly patients with multiple underlying medical conditions. All three patients died; however, the relationship of gatifloxacin to the renal failure, and the renal failure to the deaths, is unclear. In the case not presented, the reporter stated that the patient died from "an unrelated course of pneumonia, sepsis, leukemia, and congestive heart failure" 11 days after gatifloxacin was discontinued.

AERS # 3438578, Mfr # 10283745

A 62-year-old male with a history of diabetes, congestive heart failure secondary to cardiomyopathy, and renal insufficiency received gatifloxacin 400 mg every other day for infected foot ulcers. His only listed concomitant medications were furosemide and digoxin, but his physician reported verbally that metolazone had been added the day gatifloxacin was started because furosemide was becoming ineffective. Four days later, he developed anuria and was hospitalized for aggravated heart failure and **renal failure**. His creatinine level had gone from 2.8 to 6.0 (units not given). He was treated with iv furosemide and metolazone without success, and also received dobutamine. Two days after admission he experienced a hypoxic event resulting in a seizure; a brain scan and EEG remained normal. His cardiac enzymes were stated to be normal. Renal studies showed no evidence of renal artery stenosis or obstructive uropathy. Despite dialysis his heart failure got dramatically worse and multiple pressors were required. Five days after admission, he unexpectedly went into asystole; per his DNR request, no resuscitation was attempted. His cardiologists and nephrologists did not attribute his acute on chronic renal failure to gatifloxacin, but his family physician thought it was at least a possibility.

AERS # 3613878, Mfr # 10719904,

A 73-year-old male with a history of diabetes, congestive heart failure and COPD was treated with gatifloxacin for presumptive bronchitis; xrays later showed possible sinusitis and pneumonia as well. After five days he returned with no significant improvement of symptoms; he appeared weak, extremely pale, dyspneic, unsteady and tremulous. Pulse oximetry was 89-90% with room air and his BUN/creatinine were extremely elevated (100/10.8; baseline just prior to gatifloxacin therapy 33/1.4). He was hospitalized but continued to deteriorate and died 18 days later. **Acute renal failure** was listed as one of the possible causes of death. In a letter to the FDA, his physician stated that the patient had been treated with ciprofloxacin five months earlier and had experienced nausea and a slightly elevated BUN/creatinine (43/2.1) at that time, which had improved to 27/1.6 when he was switched to levofloxacin. The physician felt that although the patient had a somewhat elevated baseline BUN and multiple

medical problems which could lead to renal failure, the temporal association with the use of two fluoroquinolones indicated a possible role of the drugs in the renal disorders.

Of the ten cases reporting only effects on BUN and/or creatinine, three were primarily reports of other events (hyperglycemia, hypoglycemia, torsade de pointes), with abnormal renal function tests found on hospitalization; no baselines were given in any of the cases. In a fourth case the patient's increased creatinine was thought to have resulted from hyperosmolar nonketotic hyperglycemia (see *Cases of new-onset diabetes and profound hyperglycemic events* on pp.28-29). In another case the transplant patient's cyclosporine level appeared to have been elevated the day gatifloxacin was started. Four additional cases were poorly documented, stating only that elevated BUN and/or creatinine were seen after the patients received gatifloxacin (no evidence that baseline values were known).

The remaining case is presented below.

AERS # 3496403, Mfr # 10441277, _____

A nephrologist reported that a 63-year-old male with a history of cystic nephritis (baseline creatinine 4.9) received gatifloxacin for bronchitis. His concomitant medications (presumably chronic) were atorvastatin, quinapril, verapamil, and candesartan. After five days of gatifloxacin, the patient's creatinine had risen to 6.2 and his blood potassium was 8. He was hospitalized for three days (treatments not listed) and discharged with a normal potassium but creatinine still 6.0.

Although higher in number than the moxifloxacin cases, the gatifloxacin cases also did not provide a clear signal at this time that the drug is nephrotoxic.

H. RESPIRATORY:

The "AERS all adverse events printout" for moxifloxacin showed that 16 cases of respiratory failure had been reported for the drug. This was a surprising finding for a fluoroquinolone so all the cases were ordered for hands-on analysis; the three cases shown on the gatifloxacin printout were also ordered for comparison.

Moxifloxacin:

After eliminating duplicate cases there were nine unduplicated cases. All but one of the patients were being treated for pneumonia or acute exacerbation of chronic bronchitis. Respiratory failure in one of those eight cases was thought to be due to massive congestion from right heart failure. The respiratory failure was thought to have been caused by the patients' underlying disease in the seven other cases. The reporters who thought there was any relationship with moxifloxacin termed it a lack of effect. Two of the patients had developed respiratory failure even prior to the use of moxifloxacin.

The only report in which there was no underlying disorder thought to be the cause of the respiratory failure (AERS # 3486386) was very brief and may have omitted relevant information. A patient in her 50s was hospitalized with hypertension and respiratory failure requiring intubation within one day of starting moxifloxacin for bronchitis. The report stated that the physician was unsure whether moxifloxacin was related to the events. OPDRA attempted to contact him without success.

Gatifloxacin:

Only one of the three cases of respiratory failure was from the United States. It was the case of severe pancreatitis and nonketotic hyperosmolar hyperglycemic coma presented under **PANCREATITIS** on p.21. The original report on the case stated that the patient had also developed respiratory failure; however, that event was not mentioned in the extensive hospital records which were provided to OPDRA by the reporter.

The two remaining cases were both from Mexico. Neither patient was stated to have a history of pulmonary disease, but one was being treated for pneumonia and his physician said that gatifloxacin was not the cause of his respiratory failure. The original and followup reports on the other case had contradictory information; the original report stated that the indication for gatifloxacin was a UTI, but the followup stated "the cause of death was respiratory insufficiency due to the community acquired pneumonia".

I. SKIN:

1. BULLOUS CONDITIONS:

Dr. Meyerhoff expressed concern about cases of serious skin reactions such as Stevens-Johnson syndrome associated with moxifloxacin; she felt that these could indicate an allergenic potential of moxifloxacin (in addition to the cases of anaphylaxis and angioedema presented on pp.7-8).

AERS was searched for all cases of BULLOUS CONDITIONS reported in association with moxifloxacin or gatifloxacin. The search retrieved 16 unduplicated cases for moxifloxacin but only one for gatifloxacin. The Tequin® labeling indicates that vesiculobullous rash was reported rarely in clinical trials; as stated on p.4, Bristol-Myers Squibb has received a waiver not to submit report forms for nonserious labeled events. The Tequin® periodic report line listings were therefore reviewed to see if cases have been received by the company but not sent into AERS. There was only one case listed which might have been relevant, involving blisters on the tongue. The gatifloxacin case in AERS was primarily a report of hepatitis, but did mention scattered tiny vesicles on the patient's anterior chest and forearms which led the reporter to question an allergic reaction as the cause of the patient's hepatitis. A case of Stevens-Johnson syndrome with gatifloxacin as the suspect drug was received after the AERS search was run, and followup is being pursued. A possible confounding factor was the use of fluconazole (labeled for SJS) with no dates of administration given.

The 16 moxifloxacin cases could be categorized, starting with the most serious events, as:

toxic epidermal necrolysis	1
Stevens-Johnson syndrome	3
erythema multiforme	1
whole-body blistering	2
blistering with anaphylaxis picture (immediate onset, or with urticaria or respiratory obstruction)	5
localized blisters	4

Seven of the cases were German, six were U.S. cases, two were from Spain, and the remaining case was Swiss. There were no deaths, but five patients were hospitalized. Time to onset (after excluding the immediate onset cases listed above) ranged from two to six days in the eight cases which provided that information. Eleven of the cases were quite poorly documented, lacking information on medical history and/or concomitant medications. Most of those were foreign cases, making followup difficult.

The first seven cases listed above (the "serious skin reactions" rather than anaphylactic or nonserious events) were all potentially confounded in some way. The case of toxic epidermal necrolysis and one of the Stevens-Johnson syndrome cases were among the eleven poorly-documented cases; OPDRA called the reporter to request more information on the Stevens-Johnson syndrome case, but the followup received provided little additional documentation. Another case of Stevens-Johnson syndrome was confounded by the use of allopurinol starting only one month before moxifloxacin. In the third case of Stevens-Johnson syndrome, clotrimazole cream was prescribed the same day as moxifloxacin for an unstated reason, making dermatitis prior to the use of moxifloxacin a possibility. The case of erythema multiforme may

have been confounded by cefuroxime administration for two days just prior to starting moxifloxacin, although the skin disorder apparently did not start until day 5 of moxifloxacin administration. One of the patients who experienced whole-body blistering was stated to have leukemia, which has been associated with blistering conditions such as erythema multiforme³⁶. The reporter for the other case of whole-body blistering considered the patient's concomitant citalopram a confounding factor; however, that drug had apparently been used uneventfully by the patient for two years before starting moxifloxacin. Even if moxifloxacin cannot conclusively be identified as the cause of these cases, however, it also cannot be ruled out.

2. VASCULITIS:

Moxifloxacin:

Dr. Meyerhoff also expressed concern about moxifloxacin-associated vasculitis. AERS contained five unduplicated cases, four of which appeared primarily cutaneous in nature (involving petechial rashes, skin ulcers/erosions, and/or nail separation, or with a skin biopsy confirming vasculitis). The fifth case was a poorly-documented report to a sales representative of "vasculitis" with no other information; the FDA attempted followup on the case without success.

Additional events reported in the four well-documented cases included: edema of extremities in all four cases, chills/fever in three cases, conjunctivitis and headache in two cases each, and body aches, flushing, and proteinuria in one case each. Time to onset ranged from two to four days in the four cases; for one patient the events occurred on day three of a second course of moxifloxacin. Concomitant medications were listed on all four reports although no dates of administration were given for any of them; of the 13 drugs listed on the four reports, only naproxen lists vasculitis as an adverse reaction in its labeling and therefore may be a confounding factor since the temporal relationship is unknown.

Gatifloxacin:

AERS contained two reports of vasculitis associated with the use of gatifloxacin but neither presented much information about the nature of the event. One report was extremely scanty and did not provide information on medical history or concomitant medications, although it did indicate that the patient was hospitalized because of the reaction. The other report stated that the patient developed vasculitis, diagnosed by a dermatologist, after ten days on gatifloxacin; the only concomitant medications were diphenhydramine and fexofenadine (neither labeled for causing vasculitis).

J. SPECIAL SENSES:

1. HEARING LOSS:

Neither moxifloxacin nor gatifloxacin is labeled for causing hearing disorders, although tinnitus was reported in the clinical trials for both drugs. AERS contained no reports of hearing loss associated with gatifloxacin.

There were nine reports of hearing loss associated with moxifloxacin, but two did not provide enough information to ascertain if they were duplicate reports. Only the seven reports known to represent unduplicated cases will be discussed here.

The patients ranged in age from 48 to 76 years; there were two males and four females. (Age was unstated in three cases and gender in one.) The indication for moxifloxacin was sinusitis (a potentially confounding indication) in only two cases; the five other indications were pneumonia

³⁶ Arnold HL Jr, Odom RB, James WD. Andrews' diseases of the skin. 8th ed. WB Saunders Company, 1990;135.

(two cases), bronchitis (two cases), and fever. None of the reports listed any confounding concomitant conditions or drugs.

Time to onset of the hearing loss was listed in four cases and ranged from one day to ten days after a five-day course. None of the reports stated that the patient had complete hearing loss. Additional events were reported in six cases: tinnitus (four); vertigo/dizziness (two); nausea (two); gait disturbances (two). Four of the patients were seen by otorhinolaryngologists and/or audiologists with the following findings; "toxic damage of internal ear"; "labyrinthine deafness, pancochlear 25-30 dB"; "high grade decreased hearing left side, presbycusis right side"; "possible hearing loss in higher frequency tones in left ear".

Dechallenge information was provided in four cases. Two patients were treated with steroids and were stated to have gradually improved over three weeks in one case and three months in the other. The two other patients were stated to have not improved on followup two weeks later in one case and two months later in the other.

2. LOSS OF TASTE AND/OR SMELL:

The Avelox® labeling states only that undefined "taste perversion" occurred in clinical trials. The Tequin® labeling lists both taste perversion and taste loss, as well as parosmia.

Moxifloxacin:

AERS contained ten unduplicated cases of moxifloxacin-associated loss of taste and/or smell. Age was stated in all but one case and ranged from 39 to 64 years; there were four males and six females. The indication for moxifloxacin was sinusitis (a potentially confounding factor) in only two cases; the eight other indications were bronchitis (four cases), pneumonia (three), and unspecified "flu symptoms". One patient had diabetes but none of the other reports listed any confounding concomitant conditions.

Time to onset of the sensory disturbance was listed in eight cases and ranged from two days to shortly after what was apparently a three-week course. Six of the ten patients experienced loss of both taste and smell and three had loss of smell only. One patient did not experience loss of smell, but lost both taste and hearing; the case was also included under **HEARING LOSS** above. In three cases, the loss of taste and smell was said to be total. Five patients were seen by otorhinolaryngologists. In one of the cases, endoscopy, x-rays and CT did not reveal any pathological findings. In another, the report stated only that the physician was unable to say if the loss of taste and smell would be permanent or why it had occurred. In the third, the ENT consult stated that "hyposmia and hypogeusia were confirmed" but did not provide any other information. The fourth case was diagnosed as viral in origin but the report did not say why; in addition, "neurological clarification was recommended to exclude a central process". The specialist in the fifth case also felt that it was a "typical picture of influenza-induced anosmia".

Dechallenge information was provided in all cases. One patient improved within two days of switching from moxifloxacin to ciprofloxacin. All of the other cases, however, were persisting at the time of reporting (or followup reporting), anywhere from three weeks to three months after moxifloxacin had been discontinued.

Gatifloxacin:

AERS contained only three reports of gatifloxacin-associated loss of smell, one of which was also accompanied by loss of taste. All three patients were being treated for sinusitis, a potentially confounding factor.

Because of the Bristol-Myers Squibb waiver for nonreporting of nonserious labeled events (see p. 4), the Tequin® periodic reports were reviewed for additional cases which had not been submitted to AERS. One additional case of loss of taste was identified.

VII. SUMMARY/RECOMMENDATIONS:

Between December 1999 and April 2001, the FDA received 1209 adverse event reports for moxifloxacin and 531 for gatifloxacin (both numbers include duplicate reports). Unlabeled events were considered for review for this document if more than one or two cases had been received. The OPDRA safety evaluator discussed the printout of all adverse events with the former DSPIDP medical officer for moxifloxacin; the decision on whether to perform hands-on review of the cases was made based on the nature and severity of the event. In addition, selected other events (such as labeled events) of special concern to OPDRA and/or DSPIDP were also reviewed.

OPDRA has already recommended that a **Postmarketing** subsection be added to the **ADVERSE REACTIONS** section of the Tequin® labeling, and that hepatitis be included in the subsection. Based on the findings presented in this document, OPDRA recommends that the following additional events be added to that section: torsade de pointes, thrombocytopenia, hyperosmolar hyperglycemic nonketosis.

We recommend that the following events be added to the Avelox® **Post-Marketing Adverse Event Reports** subsection: hepatitis, _____ anemia, _____

We intend to closely monitor incoming reports of the following events, for which the AERS cases received to date are suggestive but too few in number to reach a conclusion about the role of the drug.

Gatifloxacin: interaction with coumarin anticoagulants, renal events

Moxifloxacin: interaction with coumarin anticoagulants, bullous events, vasculitis, hearing loss, loss of taste and/or smell

-/S/- August 13, 2001

Sarah J. Singer, R.Ph.

Concur:

-/S/- August 13, 2001

Debra E. Boxwell, Pharm.D.
Team Leader

cc:

NDA 21-061 / 21-062 / 21-085 / 21-277 / 21-334
HFD-590 Division File / Goldberger / Roca / Cavaille-Coll / Johann-Liang / Ibia / Meyer /
Colangelo / Anderson / Kong / Willard
HFD-440 Uhl / Boxwell / Singer / Chron / Drug

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

/s/

Sarah Singer
8/13/01 03:42:34 PM
PHARMACIST

Kathleen Uhl
8/15/01 10:46:59 AM
MEDICAL OFFICER



NDA 21-404
NDA 21-405

Bristol-Myers Squibb Company
Attention: Cynthia F. Piccirillo
Associate Director, Regulatory Science
Worldwide Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492-7660

Dear Ms. Piccirillo:

We acknowledge receipt on July 2, 2001 of your June 29, 2001 resubmissions to your new drug applications (NDAs) 21-061 for Tequin® (gatifloxacin HCl) Tablets, 200 and 400, and 21-062 for Tequin® (gatifloxacin HCl) Injection, 10 mg/ml (200 mg) 20 ml vials, 10 mg/ml (400 mg) 40 ml vials, 2 mg/ml (200 mg) 100 ml flexible container, and 2 mg/ml (400 mg) 200 ml flexible container. Please note, as Diana Willard explained by telephone on July 6, 2001 to Todd Baumgartner, M.D., M.P.H., from Bristol-Myers Squibb, that NDA numbers 21-404 (Tablets) and 21-405 (Injection) have been assigned to these resubmissions for our administrative purposes. Once a final action is taken on these resubmissions, NDA numbers 21-404 and 21-405 will be retired and all future correspondence should refer to NDAs 21-061 and 21-062, respectively.

These resubmissions contain, by reference to your February 7, 2001 submission to IND 52,081, additional data from Phase 4 studies regarding the safety of gatifloxacin hydrochloride tablets. These data were submitted to demonstrate an acceptable risk benefit profile regarding the indication of uncomplicated skin and skin structure infections in response to our December 17, 1999 action letter.

We consider these complete class 2 responses to our December 17, 1999 action letter. Therefore, the user fee goal date is January 2, 2002.

If you have any questions, call Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug
Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Ellen Frank
8/3/01 09:33:24 AM
NDA 21-404 and NDA 21-405

**Filing Meeting
August 23, 2001**

NDA Numbers: NDA 21-404
NDA 21-405

Drug Names: Tequin (gatifloxacin) Tablets (NDA 21-404)
Tequin (gatifloxacin) Injection (NDA 21-405)

Proposed Indication: Treatment of Uncomplicated Skin and Skin Structure Infections

Sponsor: Bristol-Meyers Squibb Company

Therapeutic Classification: Fluoroquinolone

Date of Applications: June 29, 2001

Date of Receipt: July 2, 2001

6 Month User Fee Goal Date: January 2, 2002 (See Regulatory Comments)

User Fee Status: None paid (See Regulatory Comments)

Submission Complete As Required Under 21 CFR 314.50? No (See Regulatory Comments)

Patent Information Included? No (See Regulatory Comments)

Exclusivity Requested? No

Debarment Statement Included? No (See Regulatory Requirements)

Financial Disclosure Information Included? No (See Regulatory Requirements)

Attendees:

Renata Albrecht, M.D.

Marc Cavaille-Coll, M.D., Ph.D.

Ekopimo Ibia, M.D.

Shukal Bala, Ph.D.

Philip Colangelo, Pharm.D., Ph.D.

Ellen Frank, R.Ph.

Diana Willard

Deputy Division Director, HFD-590

Team Leader/Medical Officer, HFD-590

Medical Officer, HFD-590

Team Leader/Microbiology, HFD-590

Clinical Pharmacology & Biopharmaceutics,
HFD-880

Chief, Project Management Staff, HFD-590

Regulatory Health Project Manager, HFD-590

Background

On December 17, 1999, an approval letter for NDAs 21-061, Tequin (gatifloxacin HCl) Tablets, and 21-062, Tequin (gatifloxacin HCl) Injection, issued, approving Tequin for community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, uncomplicated urinary tract infections, complicated urinary tract infections, pyelonephritis, and uncomplicated gonorrhea. The December 17, 1999 approval letter also stated that:

In addition, we have concluded that the indication of uncomplicated skin and skin structure infections is approvable pending submission of post-marketing data confirming the safety of gatifloxacin and therefore demonstrating an acceptable risk/benefit profile. These data will be obtained from the completion of Phase 4 commitments 1 through 6 listed below.

Phase 4 commitments 1 through 6 in the December 17, 1999 approval letter for these NDAs stated:

1. To better understand the risk/benefit profile of oral gatifloxacin, Bristol Myers Squibb will review post-marketing adverse event data following at least one million patient exposures worldwide. A substantial proportion of these exposures will be from the United States. The results of this evaluation will be submitted to the Division by December 31, 2000.
2. Bristol-Myers Squibb will conduct and submit the results of an active surveillance program. The results of this program will provide information on the incidence of adverse events for at least 15,000 patients using gatifloxacin tablets and/or gatifloxacin injection. Please submit protocols and methods for this study to the Division within ninety days of receipt of this letter. A report on this experience will be submitted to the Division by December 31, 2000.
3. Bristol-Myers Squibb will conduct a study of the effect of gatifloxacin on the QTc interval by studying its effect in patients receiving gatifloxacin in currently ongoing studies. Pre-dose and post-dose valid electrocardiograms and concurrent gatifloxacin serum concentrations should be performed. The results of this study should be submitted to the Division by December 31, 2000.
4. Bristol-Myers Squibb will conduct a gatifloxacin single oral dose escalation study of the effects on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.
5. Bristol-Myers Squibb will conduct a study to compare the effects of gatifloxacin, ciprofloxacin, clarithromycin and sparfloxacin on QTc at Cmax.

The results of this study will be submitted to the Division by December 31, 2000.

6. The pharmacokinetic studies described in items 3, 4 and 5 will include equal number of men and women over a broad range of ages (≥ 18 years; including geriatric patients).

On February 7, 2001, Bristol-Meyers Squibb Company (BMS) submitted a general correspondence to IND 52,081 that contained reports intended to satisfy the above six Phase 4 commitments. On June 29, 2001, BMS submitted to NDAs 21-061 and 21-062 a resubmission for the indication of treatment of uncomplicated skin and skin structure infections referencing the February 7, 2001 submission to IND 52,081.

Reviewer Comments and Discussion

A. Medical – Dr. Ibia

Dr. Ibia outlined the following pertaining to BMS' submission of adverse events (AEs) following the first million patient exposures worldwide:

- June 21, 1999 was the international launch date for Tequin. The launch occurred in Mexico.
- September 18, 2000 was the cut-off date for AEs listed in the February 7, 2001 submission.
- The million patient number is a rough estimate that assumes one prescription per patient.
- There were 399 spontaneous AE reports from the first million patients, 91 of which were classified as serious adverse events (SAEs).
- No literature reports of AEs were submitted in the February 7 or June 29, 2001 submissions.
- The AEs submitted exclude reports from clinical trials.

Regarding AE data for gatifloxacin-treated patients, Dr. Ibia stated that:

- 15,754 patients were enrolled at 2,795 sites. All sites were in the United States.

- Safety was based on vital signs, physical exam, and reported AEs.
- No laboratory or ECG measures were submitted except as indicated for routine patient care.
- The February 7, 2001 submission included analyses in subsets of patients at risk for arrhythmia and glucose abnormalities.
- Of the 15,754 patients that were enrolled, 18% were 65 years old or older and 60% were women.

Dr. Ibia stated that the AE profile in the current submission was generally similar to that captured on the labeling. He also noted that Sally Singer, R.Ph., of OPDRA had recently presented to the Division an update of the gatifloxacin AE data. Dr. Ibia then focused on the following AEs reported in the first one million patients exposed to gatifloxacin worldwide:

A. Cardiac:

- 3 cases of torsade de pointes/prolonged QTc
- 1 case of ventricular tachycardia/ventricular extrasystole
- 2 cases of myocardial infarctions
- 14 cases of palpitations
- 10 cases of tachycardia NOS and 2 cases of sinus tachycardia
- 2 cases of atrial fibrillation and 1 case of supraventricular tachycardia

B. Metabolism and Nutritional:

- 5 SAEs and 17 non-serious reports of hyperglycemia
- 10 SAEs and 24 non-serious reports of hypoglycemia

C. Musculoskeletal, Connective Tissue, and Bone Disorders:

- 1 SAE and 4 non-SAEs

Dr. Ibia noted that ten deaths were reported in the first million patients exposed to gatifloxacin worldwide.

Dr. Ibia stated that the following AEs have been reported for the 15,794 gatifloxacin-treated patients:

A. Cardiac:

- palpitation in $\geq 0.1\%$ of the patients
- there were similar cardiac AEs reported between those with and without increased risk for arrhythmia

Dr. Ibia noted that there were seven deaths reported in this gatifloxacin-treated group. He further stated that most of the deaths reported in the submission occurred in elderly patients with complicated medical conditions and/or multiple concomitant medications while some of the deaths were clearly unrelated to study medication.

Dr. Ibia reported the following information regarding glucose control in the 15,754 gatifloxacin-treated patients:

Adverse Event	Patients with a history of Diabetes mellitus N=1096 n (%)	Diet- Controlled N=460 n (%)	Medication- Controlled N=636 n (%)	No history of Diabetes mellitus N=14529 n (%)
Hyperglycemia	24 (2.2)	4 (0.9)	20 (3.1)	3 (<0.1)
Hypoglycemia	7 (0.6)	1 (0.2)	6 (0.9)	5 (<0.1)

Regarding blood glucose control, Dr. Ibia noted that it was difficult to make any conclusive remarks about the data presented in the table above, given that medication-controlled diabetic patients were more likely to have more severe diabetes and, perhaps, be more difficult to control.

Dr. Albrecht stated that the medical officers review of these NDAs should reflect important information regarding the patients receiving gatifloxacin, i.e., how many had underlying medical conditions, what those medical conditions were, concomitant medications, how many geriatric patients, gender of the patients, etc.

Dr. Ibia stated that the medical officers review of the original NDA data for the indication of treatment of skin and skin structure infections in NDAs 21-061 and 21-062 indicated that insufficient numbers of patients with the diagnoses of impetiginous lesions and erysipelas were studied to be able to draw any conclusions regarding safety and efficacy for these indications. The approvability of these indications will be re-examined after the review of the data submitted in NDAs 21-404 and 21-405.

Dr. Ibia summarized that, from an initial cursory review, these NDAs do not present any new safety concerns.

From the medical Officers' perspective, these new drug applications are fileable.

B. Statistical – Dr. Higgins

An August 15, 2001 E-mail from Dr. Higgins notes that Dr. Silliman's review of the data for the indication of treatment of skin and skin structure infections in NDAs 21-061 and 21-062 concluded that the "efficacy results for study 420-005 are fairly robust and suggest that gatifloxacin is similar to levofloxacin in terms of efficacy." Dr. Higgins' E-mail further states that there most probably is no need for an additional statistical review for the proposed indication in these NDAs but added that the statistical reviewers are available to work with the review team for if statistical questions/concerns arise.

There are no statistical issues that would preclude filing of these new drug applications.

C. Microbiology – Dr. Bala

These applications are fileable from the microbiologists' perspective.

D. Clinical Pharmacology and Biopharmaceutics – Dr. Colangelo

Dr. Colangelo stated that he has reviewed the data submitted on February 7, 2001. His written review is still in draft. He noted that there was not a large number of patients age 65 or over in the data submitted.

These supplemental applications are fileable from the clinical pharmacology and biopharmaceutics perspective.

Regulatory Comments

The August 3, 2001 acknowledgement letter for NDAs 21-404 and 21-405 states:

We acknowledge receipt on July 2, 2001 of your June 29, 2001 resubmissions to your new drug applications (NDAs) 21-061 for Tequin® (gatifloxacin HCl) Tablets, 200 and 400 mg, and 21-062 for Tequin® (gatifloxacin HCl) Injection, 10 mg/ml

(200 mg) 20 ml vials, 10 mg/ml (400 mg) 40 ml vials, 2 mg/ml (200 mg) 100 ml flexible container, and 2 mg/ml (400 mg) flexible container. Please note, as Diana Willard explained by telephone on July 6, 2001 to Todd Baumgartner, M.D., M.P.H., from Bristol-Myers Squibb, that NDA numbers 21-404 (Tablets) and 21-405 (Injection) have been assigned to these resubmissions for our administrative purposes. Once a final action is taken on these resubmissions, NDA numbers 21-404 and 21-405 will be retired and all future correspondence should refer to NDAs 21-061 and 21-062, respectively.

These resubmission contain, by reference to your February 7, 2001 submission to IND 52,081, additional data from Phase 4 studies regarding the safety of gatifloxacin hydrochloride tablets. These data were submitted to demonstrate an acceptable risk benefit profile regarding the indication of uncomplicated skin and skin structure infections in response to our December 17, 1999 action letter.

We consider these complete class 2 responses to our December 17, 1999 action letter. Therefore, the user fee goal date is January 2, 2002.

There is a six month User Fee Goal Date for these administrative NDAs as the June 29, 2001 submissions, as stated in the acknowledgement letter, are Class 2 resubmissions.

No User Fee was paid for NDAs 21-404 and 21-405 as the indication proposed in these applications was originally reviewed under NDAs 21-061 and 21-062 (User Fees were paid for NDAs 21-061 and 21-062) and because the June 29, 2001 submission is a resubmission in response to the December 17, 1999 approval letter for NDAs 21-061 and 21-062.

No debarment statement or financial disclosure information was included in the June 29, 2001 submission as the data to be reviewed involved no new investigators (from the investigators listed in NDAs 21-061 and 21-062).

No patent information was included in the June 29, 2001 submission as there is no new patent information to be reported from that provided in NDAs 21-061 and 21-062.

Summary

It was agreed that these applications are acceptable for filing.

Minutes Preparer: _____
Diana Willard

Meeting Chair: _____
Renata Albrecht, M.D.

NDA 21-404
NDA 21-405
August 23, 2001
Page 9

blank page

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

/s/

Renata Albrecht
1/31/02 03:19:38 PM

Application Information

NDA 21-404 NDA 21-405	Efficacy Supplement Type SE1 (NOTE: The USSSI indication for Tequin was "approvabled" in the December 17, 1999 approval letter for NDAs 21-061 and 21-062. The June 29, 2001 resubmissions for the USSSI indication were assigned NDA numbers 21-404 and 21-405 for the Division's administrative purposes {see August 3, 2001 acknowledgement letter}.)	Supplement Number
Drug: Tequin (gatifloxacin HCl) Tablets Tequin (gatifloxacin HCl) Injection		Applicant: Bristol-Myers Squibb Company
RPM: Diana Willard	HFD-590	Phone # 301-827-2127
Application Type: (X) 505(b)(1) () 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	<input checked="" type="checkbox"/> Standard () Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 	<input type="checkbox"/> 6 (new indication)	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 	N/A	
❖ User Fee Goal Date	February 26, 2003	
❖ Special programs (indicate all that apply)	<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee (NOTE: See Page 8 of the August 23, 2001 Filing Meeting Minutes) 	<input checked="" type="checkbox"/> Paid (NDA 21-061 and NDA 21-062)	
<ul style="list-style-type: none"> • User Fee waiver 	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
<ul style="list-style-type: none"> • User Fee exception 	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<ul style="list-style-type: none"> • This application is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<ul style="list-style-type: none"> • Exception for review (Center Director's memo) 	N/A	
<ul style="list-style-type: none"> • OC clearance for approval 	N/A	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. (NOTE: See Page 8 of the August 23, 2001 Filing Meeting Minutes)	<input checked="" type="checkbox"/> Verified (Debarment Certification in NDA 21-061 and NDA 21-062)	
❖ Patent		
<ul style="list-style-type: none"> • Information: Verify that patent information was submitted (NOTE: See Page 8 of the August 23, 2001 Filing Meeting Minutes) 	<input checked="" type="checkbox"/> Verified (Patent Information in NDA 21-061 and NDA 21-062)	
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify type of certifications submitted 	21 CFR 314.50(I)(1)(I)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(I)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) N/A	

<ul style="list-style-type: none"> For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). 	<input type="checkbox"/> Verified N/A
❖ Exclusivity Summary (approvals only)	X (December 17, 2002)
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	X (August 23, 2001 Filing Meeting Minutes – under Meeting Minutes tab in Action Package)
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	December 17, 1999/AE action December 21, 2001/AE action August 2, 2002/AE action
<ul style="list-style-type: none"> Status of advertising (approvals only) 	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public Communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	X (clean and annotated from submissions dated: September 30, 2002 February 6, 2002 June 29, 2001)
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X (See NDA 21-061- and NDA 21-062)
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) 	X (DDMAC review dated December 14, 2001 and ODS review dated June 14, 2002)
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 2 in class) 	X
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Applicant proposed 	N/A
<ul style="list-style-type: none"> Reviews 	N/A
❖ Post-marketing commitments	

• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ * Outgoing correspondence (i.e., letters, E-mails, faxes, memoranda, telecons)	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X (October 7, 1997: See NDA 21-061 and NDA 21-062)
• Pre-NDA meeting (indicate date)	X (April 3, 1998: See NDA 21-061 and NDA 21-062)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X (Filing Meeting: August 23, 2001)
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X (Division Director memo dated October 28, 2002 and ODS memos dated December 10, 2001, August 15, 2001, and July 13, 2000)
✓ Clinical reviews (indicate date for each review)	February 7 and August 12, 2002 (See also NDA 21-061 and 21-062)
✓ Microbiology (efficacy) review (indicate date for each review)	October 22, 2001
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
OK ❖ Statistical review(s) (indicate date for each review) (NOTE: Dr. Higgins, Biostatistics Team Leader, wrote in an August 15, 2001 E-mail to Ms. Diana Willard, HFD-590 Project Manager, that Dr. Silliman's review of the data for the indication of treatment of skin and skin structure infections in NDAs 21-061 and 21-062 concluded that the "efficacy results for Study 420-005 are fairly robust and suggest that gatifloxacin is similar to levofloxacin in terms of efficacy." Dr. Higgins' E-mail further stated that there most probably is no need for an additional statistical review for the proposed indication for NDAs 21-404 AND 21-405.)	X (NDA 21-061 and NDA 21-062)
✓ Biopharmaceutical review(s) (indicate date for each review)	August 12 and 15, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	N/A
❖ Environmental Assessment	

• Categorical Exclusion (<i>indicate review date</i>)	N/A
• Review & FONSI (<i>indicate date of review</i>)	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
• Micro (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	N/A
• Facilities inspection (provide EER report)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation N/A
• Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested N/A
Nonclinical Pharm/Tox Information	
Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	N/A
Nonclinical inspection review summary	N/A
Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
CAC/ECAC report	N/A

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

/s/

Diana Willard
6/5/03 08:13:43 AM

NDA/ANDA # 021404 Supp # 000

Trade Name TEQUIN (GATIFLOXACIN) 200/400MG TABLETS

Generic name _____

Drug Type 6

Approving Division 590

Initial approval 10/17/2002

6 Week Dat _____

Comments

Letter Information

Date Letter Rec'd 10/18/2002

Letter Redactions Started # _____

Letter Redaction Finished #1 _____

CSO #1 - Letter _____

Letter Redactions Started # _____

Letter Redaction Finished #2 _____

CSO #2 - Letter _____

10/18/2002

TAUB

Date to M _____

Date on Web _____

10/21/2002

10/21/2002

Label Information

Label on Web 10/18/2002

Package Review Information

Reviews Rec'd in DIDP 6/12/2003

Review Redact 1 Started 6/14/06

Review Redact 1 Completed 6/29/06

CSO #1 - Package Medina

Review 2 Redact Started _____

Review Redact 2 Completed _____

CSO #2 - Package _____

Date to Scanne _____

Date from Scanner _____

Date to ML _____

Date on Web _____

