CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-404

21-405

21-061/s010, s016

21-062/s011, s017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

Bristol-Myers Squibb
Pharmaceutical Research Institute
Attention: Joan Fung-Tomc, Ph.D.
Director, Regulatory Science
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Fung-Tomc:

Please refer to your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tequin® (gatifloxacin HCl) Tablets, 200 mg and 400 mg (NDAs 21-061 and 21-404) and 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 (NDA 21-062 and 21-405).

1. NDA 21-404 and 21-405

NDAs 21-061 and 21-062, originally submitted on December 28, 1998, were approved on December 17, 1999 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 further 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." For our administrative purposes, we assigned NDA numbers 21-404 (Tequin Tablets) and 21-405 (Tequin Injection) for the indication of treatment of uncomplicated skin and skin structure infections. Your submissions of June 29, 2001 to these NDAs constituted a complete response to our December 17, 1999 approvable letter. A second approvable letter was issued for NDAs 21-404 and 21-405 on December 21, 2001. Your submissions of February 6, 2002 constituted a complete response to our December 21, 2001 approvable letter. A third approvable letter was issued for NDAs 21-404 and 21-405 on August 2, 2002.

Your submissions of August 23, 2002 constituted a complete response to our August 2, 2002 approvable letter.

We acknowledge receipt of your submissions dated August 9 and September 30, 2002.

NDAs 21-404 and 21-405 provide for the use of Tequin® Tablets and Tequin® Injection for the treatment of uncomplicated skin and skin structure infections.

2. NDA 21-061/S-010 and NDA 21-062/S-011

Please also refer to your supplemental new drug applications dated July 20, 2001, received July 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. An approvable letter was issued for NDA 21-061/S-010 and NDA 21-062/S-011 on December 21, 2001. Your submissions of May 28, 2002 constituted a complete response to our December 21, 2001 approvable letter. A second approvable letter was issued for these supplements on August 2, 2002.

Your submissions of August 23, 2002 constituted a complete response to our August 2, 2002 approvable letter.

We acknowledge receipt of your submissions dated August 9 and September 30, 2002.

These supplemental new drug applications provide for revisions to the Tequin® package insert to add information regarding QTc prolongation.

3. NDA 21-061/S-016 and NDA 21-062/S-017

Please also refer to your supplemental new drug applications dated May 10, 2002, received May 13, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. An approvable letter was issued for NDA 21-061/S-016 and NDA 21-062/S-017 on August 2, 2002.

Your submissions of August 23, 2002 constituted a complete response to our August 2, 2002 approvable letter.

We acknowledge receipt of your submissions dated July 29, August 9, and September 30, 2002.

These "Changes Being Effected" supplemental new drug applications provide updated information regarding disturbances in glucose homeostasis in the CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ANIMAL PHARMACOLOGY, and Patient Package Insert sections of the package insert. These supplemental NDAs further provide for a change in the generic name from "gatifloxacin" to "gatifloxacin in 5% dextrose" and revisions to the labeling header and the DESCRIPTION, DOSAGE AND ADMINISTRATON, and HOW SUPPLIED sections of the package insert to reflect this change. In addition, these supplemental NDAs propose revisions to the artwork for both the primary bag and the overwrap for the Tequin® Injection minibags to reflect the change in generic name from "gatifloxacin" to "gatifloxacin in 5% dextrose."

We have completed the review of these applications (NDA 21-404, NDA 21-405, NDA 21-061/S-010, NDA 21-061/S-016, NDA 21-062/S-011, and NDA 21-062/S-017), as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate container [primary bag and overwrap] submitted July 29, 2002).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL to each supplement as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, these submissions should be designated **"FPL for approved NDA 21-404, NDA 21-405, NDA 21-061/S-010, NDA 21-062/S-011, NDA 21-061/S-016, and NDA 21-062/S-017."** Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on the information submitted, we conclude the following:

For the use of Tequin® Tablets and Tequin® Injection for the treatment of uncomplicated skin and skin structure infections, we are deferring submission of pediatric studies for patients ages from birth through 16 years of age until January 2007.

In addition, we request that you submit three copies of the introductory promotional materials you propose to use for these products for the treatment of uncomplicated skin and skin structure infections. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to NDAs 21-061 and 21-062 and a copy to the following address:

MEDWATCH, HF-2
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). With the approval of administrative NDAs 21-404 and 21-405, these NDA numbers will be retired. All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDAs 21-061 and 21-062 for these drug products. In the future, please do not make submissions to NDAs 21-404 and 21-405 except for the final printed labeling requested above.

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

Sincerely,

{See appended electronic signature page}

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/

Renata Albrecht
10/17/02 03:47:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-404

21-405

21-061/s010, s016

21-062/s011, s017

APPROVABLE LETTER 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

Bristol-Myers Squibb
Attention: Joan Fung-Tomc, Ph.D.
Director, Regulatory Science
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Fung-Tomc:

Please refer to your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tequin® (gatifloxacin HCl) Tablets, 200 mg and 400 mg (NDAs 21-061 and 21-404) and 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 (NDAs 21-062 and 21-405).

1. NDA 21-404 and NDA 21-405

NDAs 21-061 and 21-062, originally submitted on December 28, 1998, were approved on December 17, 1999 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 further 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." For our administrative purposes, we assigned NDA numbers 21-404 (Tequin Tablets) and 21-405 (Tequin Injection) for the indication of treatment of uncomplicated skin and skin structure infections. Your submission of June 29, 2001 to these NDAs constituted a complete response to our approvable letter of December 17, 1999. A second approvable letter was issued for NDAs 21-404 and 21-405 on December 21, 2001.

Your submissions of February 6, 2002 constituted a complete response to our December 21, 2001 action letter for these NDAs.

We acknowledge receipt of your submissions dated April 4 and April 16, 2002. We also acknowledge receipt of your July 29, 2002 submissions to INDs 52,081, 53,521, and 52,672.

NDAs 21-404 and 21-405 propose the use of Tequin® Tablets and Tequin® Injection for the treatment of uncomplicated skin and skin structure infections.

2. NDA 21-061/S-010 and NDA 21-062/S-011

Please also refer to your supplemental new drug applications dated July 20, 2001, received July 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. An approvable letter was issued for NDA 21-061/S-010 and NDA 21-062/S-011 on December 21, 2001.

Your submissions of May 28, 2002 constituted a complete response to our December 21, 2001 action letter for these supplemental NDAs.

These supplemental new drug applications propose revisions to the Tequin® package insert to add information regarding QTc prolongation.

3. NDA 21-061/S-016 and NDA 21-062/S-017

Please also refer to your supplemental new drug applications dated May 10, 2002, received May 13, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

We acknowledge receipt of your submissions dated May 28, 2002.

We also acknowledge receipt of your submissions dated July 29, 2002. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

These "Changes Being Effected" supplemental new drug applications provide updated information regarding disturbances in glucose homeostasis in the CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ANIMAL PHARMACOLOGY, and Patient Package Insert sections of the package insert. These supplemental NDAs further provide for a change in the generic name from "gatifloxacin" to "gatifloxacin in 5% dextrose" and revisions to the labeling header and the DESCRIPTION, DOSAGE AND ADMINISTRATON, and HOW SUPPLIED sections of the package insert to reflect this change. In addition, these supplemental NDAs propose revisions to the artwork for both the primary bag and the overwrap for the Tequin® Injection minibags to reflect the change in generic name from "gatifloxacin" to "gatifloxacin in 5% dextrose."

We have completed the review of these applications (NDA 21-404, NDA 21-405, NDA 21-061/S-010, NDA 21-061/S-016, NDA 21-062/S-011, and NDA 21-062/S-017), as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to:

- 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.

In addition, it will be necessary for you to submit draft labeling identical in content to the enclosed labeling (text for the package insert). To facilitate review of your submissions, please provide a highlighted or marked-up copy that shows the changes that are being made. It will also be necessary for you to reference your July 29, 2002 submission that contained the artwork for the primary bag for the Tequin® Injection minibags. If additional information relating to the safety or effectiveness of gatifloxacin becomes available, revisions of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action the FDA may proceed to withdraw these applications. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as major amendments nor will the review clock be reactivated until all deficiencies have been addressed.

These drug products may not be legally marketed for this indication until you have been notified in writing that these applications (NDA 21-404 and NDA 21-405) are approved.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

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
8/2/02 12:12:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-404

21-405

21-061/s010, s016

21-062/s011, s017

APPROVABLE LETTER 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

Bristol-Myers Squibb
Attention: Joan Fung-Tomc, Ph.D.
Director, Regulatory Science
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Fung-Tomc:

Please refer to your new drug applications (NDAs 21-061 and 21-062) dated December 28, 1998, received December 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tequin® (gatifloxacin HCl) Tablets, 200 mg and 400 mg (NDA 21-061) and 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 (NDA 21-062).

Your submissions of June 29, 2001 constituted a complete response to our December 17, 1999 action letter. NDA numbers 21-404 (Tequin® Tablets) and 21-405 (Tequin® Injection) were assigned to these submissions for our administrative purposes.

We acknowledge receipt of your submissions dated July 30, August 6, and December 11, 2001.

NDAs 21-404 and 21-405 provide for the use of Tequin® Tablets and Tequin® Injection for the treatment of uncomplicated skin and skin structure infections.

Please also refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
Tequin® (gatifloxacin HCl) Tablets	NDA 21-061	S-010	July 20, 2001	July 23, 2001
Tequin® (gatifloxacin HCl) Injection	NDA 21-062	S-011	July 20, 2001	July 23, 2001

Supplemental NDAs 21-061/S-010 and 21-062/S-011 provide for revisions to the Tequin package insert to add information regarding QTc prolongation based on data collected to address Phase IV commitments pertaining to QTc as outlined in the December 17, 1999 approval letter for NDAs 21-061 and 21-062.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling revised as enclosed.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL to each NDA, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of gatifloxacin becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDAs by submitting all safety information you now have regarding gatifloxacin. The safety update should include data from all nonclinical and clinical studies of gatifloxacin regardless of indication, dosage form, or dose level as well as data from worldwide postmarketing experience.

1. Describe in detail any significant changes or findings in the safety profile.

2. Present a retabulation when assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporating new safety data. Describe any new trends or patterns identified.

3. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

4. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the data in the original NDAs.

5. Provide a summary of worldwide experience on the safety of gatifloxacin. Include an updated estimate of use for gatifloxacin marketed in other countries.

6. Provide English translations of current approved foreign labeling not previously submitted.

In addition, we have received your submission dated February 7, 2001 (IND 52,081). This submission and your June 29, 2001 (NDAs 21-404 and 21-405) complete response to our December 17, 1999 action letter reported on the following postmarketing study commitments:

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).

We have reviewed your submissions and conclude that the above commitments were fulfilled.

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw these applications. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as major amendments nor will the review clock be reactivated until all deficiencies have been addressed.

These drug products may not be legally marketed for this indication until you have been notified in writing that these applications are approved.

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

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting 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/

Renata Albrecht
12/21/01 11:18:12 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-404

21-405

21-061/s010, s016

21-062/s011, s017

APPROVABLE LETTER 1

NDA 21- 061
NDA 21-062

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Douglas C. Kriesel, Ph.D.
Director, Worldwide Regulatory Affairs
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Dr. Kriesel:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tequin™ (gatifloxacin) Tablets, 200mg and 400mg, and Tequin™ (gatifloxacin) Injection, 10mg/mL (200mg) 20mL vials, 10mg/mL (400mg) 40mL vials, 2mg/mL (200mg) 100-mL flexible container, and 2mg/mL (400mg) 200-mL flexible container.

We acknowledge receipt of your submissions dated:

December 28, 1998
January 27, 1999
January 29, 1999
February 5, 1999
February 10, 1999 (2)
February 12, 1999
March 19, 1999
March 23, 1999
April 7, 1999
April 9, 1999
April 16 1999
May 5, 1999
May 10, 1999
May 27, 1999
June 11, 1999
July 12, 1999
July 13, 1999
July 20 ,1999
July 21 1999
August 6, 1999
August 12, 1999
August 13, 1999
August 20, 1999
August 25, 1999
August 27, 1999
September 2, 1999
September 3 ,1999
September 16, 1999
September 21 ,1999
September 21, 1999
September 24, 1999
October 8, 1999 (3)
October 22, 1999
October 29, 1999
November 2, 1999
November 4, 1999
November 22, 1999
December 3, 1999 (2)
December 8, 1999 (2)
December 10, 1999
December 14, 1999
December 15, 1999
December 16, 1999 (2)
December 17, 1999 (2)

These new drug applications provide for the use of Tequin™ (gatifloxacin) for Community-Acquired Pneumonia; Acute Bacterial Exacerbation of Chronic Bronchitis; Acute Sinusitis; [ ]; Uncomplicated Urinary Tract Infections; Complicated Urinary Tract Infections and Pyelonephritis; Uncomplicated Urethal, Pharyngeal, and Rectal Gonorrhea in Males; as well as Endocervical, Pharyngeal, and Rectal Gonorrhea in Females.

We have completed the review of these applications, as amended. We have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling submitted December 17, 1999, 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. Accordingly, the applications are approved effective on the date of this letter.

In addition, we have concluded that the indication of [ ] 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 completion of Phase 4 commitments 1 through 6 listed below.

The Phase 4 commitments to which Bristol-Myers Squibb Company agreed in its submission dated December 16, 1999, along with any completion dates agreed upon, are listed below:

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 ($\geq$18 years; including geriatric patients).

7. Bristol-Myers Squibb will repeat the rat oral and intravenous teratology studies using adequately high dose levels. The results of these studies will be submitted to the Division by December 31, 2000.

The Division anticipates discussing the details of the above studies at your earliest convenience.

Protocols, data, and final reports for the Phase 4 commitments should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition to the above Phase 4 commitments, we suggest that Bristol Myers Squibb consider conducting the following studies:

1.

2.

3.

4.

The final printed labeling (FPL) must be identical to the submitted labeling dated December 17, 1999 (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-061 and NDA 21-062". Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact D. Laurie Bernato, R.N., MN, Regulatory Project Manager, at (301) 827-2127.

Sincerely yours,

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure