DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE CONFERENCE

DATE OF MEETING: February 13, 1998

INDs: [redacted]

Drugs: Oral Gatifloxacin

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute

Subject: Protocol AI420-052 - A Follow-up, Pilot Study of the Infection-Free Interval Following Treatment of Acute Exacerbation of Chronic Bronchitis

Meeting Chair: Marianne Mann, M.D.
Sponsor Chair: Douglas C. Kriesel, Ph.D.
Project Manager: Brenda Atkins

FDA Attendees, Titles, and Offices:
Marianne Mann, M.D., Acting Medical Team Leader
Brenda Atkins, Project Manager

External Constituents and Titles:
Phillip F. Pierce, M.D., Medical Monitor, Infectious Diseases Clinical Research
Douglas Kriesel, Ph.D., Worldwide Regulatory Affairs (Liaison)

Background:
Bristol-Myers Squibb Pharmaceuticals (BMS) submitted the subject protocol dated January 27, 1998, received January 28, 1998, for review and comment. Upon her review of this protocol, Dr. Marianne Mann requested clarification as to what purposes this study would be used in the approval process for gatifloxacin. This teleconference was held to discuss this issue.

Objectives:

To discuss the purpose of the subject study.

Discussion:

1. The sponsor stated that the objectives of conducting the pilot study were the following:

   a. to validate the quality of life SF12 survey; and

b. if significant differences were found between gatifloxacin and other antibiotics regarding infection free intervals, that they might consider this a labeling claim.

Action/Outcome:

1. Dr. Mann stated that if this study showed dramatic differences, we could work with the sponsor to validate this data as a labeling claim by designing a more controlled study; but protocol AI420-052 by itself would most likely not be sufficient to support a labeling claim.

2. Other additional information obtained during this teleconference were that the sponsor will request a pre-NDA meeting some time between the end of March or within the first 2 weeks of April 1998. NDAs for both oral and IV gatifloxacin will be filed in December 1998.

3. The FDA will attempt to get more definitive information regarding an E-mail encryption system. The project manager will again contact Greg Brolund from the Office of Information Technology (OIT).

concurrence: /S/ 2/13/98
HFD-590/ActingTL/MMann/
HFD-590/CSO/BAtkins/drafted 021398
CC:
[redacted]
Division file
HFD-590/ActingTL/MMann
HFD-520/PHARM/AEllis
HFD-590/MICRO/~~PDionne~~
HFD-880/BIOPHARM/PColangelo
HFD-590/CHEM/GHolbert
HFD-590/STAT/NSilliman
HFD-590/CSO/BAtkins

Record of Telephone Conference

Address: [redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Meeting Date: April 3, 1998 **Time: 1:30** **Location: N426**

IND Numbers and Drug Name: [redacted] **Gatifloxacin for Oral Use**
[redacted] **Gatifloxacin for Intravenous (IV) Use**

External meeting requestor: Bristol-Myers Squibb Company

Type of Meeting: Pre-NDA meeting

Meeting Chair: Marianne Mann, M.D. **Sponsor Chair:** Douglas Kriesel, Ph.D.

Meeting Recorder: Brenda J. Atkins, Project Manager

FDA Attendees, Titles, and Offices:

Dianne Murphy, M.D., ODE IV Director
Mark Goldberger, M.D., M.P.H, Director, DSPIDP
Renata Albrecht, M.D., Deputy Director, DSPIDP
Marc Cavaille-Coll, M.D., Medical Team Leader, DSPIDP
Brad Leissa, M.D., Medical Team Leader, DSPIDP
Robert Hopkins, M.D., Medical Team Leader, DSPIDP
Marianne Mann, M.D., Medical Officer, DSPIDP
Joyce Korvick, M.D., Medical Officer, DSPIDP
Rigoberto Roca, M.D., Medical Officer, DSPIDP
Aloka Chakravarty, Ph.D., Acting Statistical Team Leader
Gene Holbert, Ph.D., Chemist Reviewer, DSPIDP
Funmilayo Ajayi, Ph.D., Biopharmaceutics Team Leader, DSPIDP
Philip Colangelo, Pharm.D., Ph.D., Biopharmaceutics Reviewer, DSPIDP
Steve Hundley, Ph.D., Pharmacology Reviewer, DSPIDP
Amy Ellis, Ph.D., Pharmacology Reviewer, DSPIDP
Sheryl Lard, Ph.D., Microbiology Team Leader, DSPIDP
Peter Dionne, Microbiology Reviewer, DSPIDP
Antoine El Hage, Ph.D., Pharmacologist, Office of Compliance,
Division of Scientific Investigations, Clinical Investigations Branch
Brenda J. Atkins, Project Manager, DSPIDP

External Constituent and Titles:

Claude Nicaise, M.D.,Executive Director, Infectious Diseases Clinical Research
Jeanne Breen, M.D., Director, Infectious Diseases Clinical Research
Howard Mayer, M.D., Associate Director, Infectious Diseases Clinical Research
Roger M. Echols, M.D., Vice-President, Infectious Diseases Clinical Research

Dennis Grasela, Pharm.D., Ph.D., Associate Director, Human Pharmacology
Janis Grechko, Ph.D., Director, Biostatistics and Data Management
Mohan S. Beltangady, Ph.D., Director, Biostatistics and Data Management
Judith Goldberg, Ph.D., Vice-President, Biostatistics and Data Management
Daniel P. Bonner, Ph.D., Executive Director, Microbiology
Randolph A. Soltys, Ph.D., Director, Toxicology
Frank LaCreta, Ph.D., Senior Research Investigator, Metabolism and Pharmacokinetics
Laura Barrow, Pharm.D., Director, Project Planning and Management
Anthony Santopolo, M.D., Vice-President, Worldwide Regulatory Affairs
Satyam Upadrashta, Ph.D., Manager, Worldwide Regulatory Affairs (CMC)
John M. Joseph, Director, Worldwide Regulatory Affairs (Operations)
Hugh McIlhenny, Ph.D., Director, Worldwide Regulatory Affairs (Liaison)
Douglas Kriesel, Ph.D., Director, Worldwide Regulatory Affairs (Liaison)

Background:
On February 17, 1998, the sponsor requested a face-to-face pre-NDA meeting with FDA representatives in the Division of Special Pathogen and Immunologic Drug Products. The requested meeting dates were for either April 3, or April 9, 1998. The meeting request date of April 3, 1998, was confirmed via facsimile dated March 2, 1998. A decision was made to have a telephone conference with the company rather than a face-to-face meeting given that the sponsor's drug development plans presented nothing significantly alarming. The background meeting packages were received on March 13, 1998, and provided an update on the clinical program and a list of items for discussion. The package also contained draft Tables of Contents for both Gatifloxacin Tablets and Gatifloxacin IV New Drug Applications (NDA), a draft copy of the Phase 2 clinical study report for AI420-004 (bronchitis), the analysis plan used to prepare this report, and a copy of the analysis plan for the Phase 3 uncomplicated UTI study, AI420-010.

On April 2, 1998, the sponsor provided an updated "Items for Discussion at the Gatifloxacin pre-NDA Teleconference" that included an additional discussion item not previously included in the meeting background package dated March 12, 1998.

Meeting Objectives:
1. To provide the sponsor with guidance regarding the drug development program for Gatifloxacin Oral and Gatifloxacin IV NDAs to be submitted December 1998.
2. To provide the sponsor further FDA guidance regarding unresolved issues that may require further development in support of a NDA submission.

Agenda items:
DISCUSSION ITEMS:
1. Criteria for having an indication for community acquired pneumonia (CAP) caused by *S. Pneumoniae* that includes the statement "including cases associated with concurrent bacteremia".
2. Acceptability of sponsor's approach in submitting drug-drug interaction studies.
3. Acceptability of sponsor's approach in submitting tissue distribution studies.

4. Acceptability of submitting study results data from a study investigating the mechanism for the local reactions noted with the IV administration of gatifloxacin along with the IV safety experience from the Phase III program to obtain approval for marketing the IV formulation.
5. Acceptability of submitting data from clinical studies under the sponsor's Phase IIIB program using the IV dosage form in the 120-day safety update and/or the final review safety update.
6. FDA requirements in reference to the final rule effective February 2, 1999, requiring the sponsor to submit financial disclosure certification for clinical investigators.
7. Acceptability of submitting all clinical and most of the preclinical data for both the IV and tablet NDA in only the submission for the tablet NDA and cross-referencing to the IV NDA.

DISCUSSIONS:
FDA representatives provided the following responses to the discussion items listed above:

1. Given the current low numbers of patients (possibly a total of nine) with CAP caused by *S. pneumoniae* and associated with concurrent bacteremia, it was suggested that the sponsor increase patient numbers. Since the study will remain open until November 1998, there is opportunity for additional increases in overall numbers of patients, which will provide more data for the FDA to base their decision. After the FDA has been presented with this data and the criteria for claiming this indication on the labeling has been more succinctly defined, the FDA will be in a better position to advise the sponsor with a more definitive decision on this matter.

2. The approach proposed by the sponsor in submitting in vivo drug-drug interaction studies are acceptable to the FDA. Method validation reports and individual run data for standard curves and quality control specimens will be provided by the respective sponsors and submitted to the NDA.

   The sponsor reported that based on the lack of interaction *in vitro* between gatifloxacin and CYP3A4 substrates and the near complete elimination of gatifloxacin via the kidney, that they would request general labeling for CYP3A4 substrates should the anticipated lack of interaction be confirmed in the midazolam study. The FDA advised that a review of both *in vitro* and *in vivo* data will be done upon receipt of data from the midazolam study and a determination will be made.

3. The sponsor was informed that for labeling purposes tissue distribution data should only be relevant to indications identified in the NDAs. Thus, the tissue distribution data from, for example, the gingiva and the eye, would appear to not be relevant for the proposed indications sought for in the NDAs. The sponsor was also informed that adequate documentation of the validation and performance of all assay methods used to determine the concentrations of gatifloxacin in the various tissues/fluids needs to be provided with the respective study reports. In response to the sponsor's inquiry regarding the number of tissue specimens that would be needed for inclusion into the label, the sponsor was informed that the Agency would ideally like to see six or more tissue level determinations for each timepoint. The range of the individual tissue:serum

ratios and/or standard deviation about the mean should also be reported along with the mean values of the tissue:serum ratios.

4. The approach to perform *in vitro* based assessments of histamine release from human basophils, and to perform an *in vivo* study in healthy volunteers to assess the mechanism of local reactions noted with gatifloxacin and to submit this information along with the IV safety experience from the Phase III program in the 120-day updates to obtain approval for marketing the IV formulation is suitable and reasonable. The numbers of patients to be evaluated (160 patients) is adequate assuming no bioequivalence issues arise. Any additional reports of hypoglycemic cases would be an issue.

5. Submission of data from clinical studies under the sponsor's Phase IIIB program using the IV dosage form in the 120-day update and/or the final review safety update is acceptable. This data can be expected in October or November 1999. These clinical studies are for indications, i.e, pelvic inflammatory disease and nosocomial pneumonia, that were not included in the seven indications in the sponsor's original NDAs for oral and IV gatifloxacin. The sponsor anticipates a supplemental NDA submission for these indications in the future.

6. The sponsor was advised that a response from the General Counsel's office is pending regarding the February 2, 1998, final rule requiring sponsors of any drug to submit financial disclosure information on their clinical investigators. It is not known if the sponsor will be subjected to the rule given that their NDA has been submitted to the FDA prior to the effective date (February 2, 1999). The sponsor will be informed of this as soon as a response has been received from the General Counsel. The sponsor stated that this requirement of collecting this information would create extra time constraints.

7. Submission of all clinical and most of the preclinical data for both the IV and tablet NDA in only the submission for the tablet NDA and cross-referenced to the IV NDA is acceptable as long as all data is available and easily accessible.

Unresolved issues or issues requiring further discussion:

1. Establishment of criteria for various indications, particularly CAP caused by *S. pneumoniae* are currently undergoing discussions among the Division of Special Pathogen and Immunologic Drug Products and other divisions to ensure consistency. The sponsor will be informed of any new developments that pertain to the various indications being pursued.

2. The sponsor will be informed when the General Counsel renders its response to their question regarding FDA requirements for submitting financial disclosure information on their clinical investigators as it pertains to their situation as soon as possible.

[redacted]
Gatifloxacin Oral and IV

Decisions (agreements reached):

1. The table of contents to the NDAs will be revised under the "Section 8/10 - Clinical/Statistical Data" section listing pivotal trials first with supportive trials following.

2. The NDAs submission target dates are still on course for December 1998.

3. Analytical plans for the various indications will be finalized and submitted in the next few weeks and individual teleconferences for each may be warranted. Additional clinical study reports to be submitted to the application are also forthcoming.

4. The format of the integrated summary data will be submitted within the next month or two in draft.

5. Additional data on the hypoglycemic, hyperglycemic, and seizure patients will be provided by the sponsor.

Signature, minutes preparer: /s/ 5/13/98
Concurrence Chair: /s/ 5/13/98

Attachments/Handouts

Decisions (agreements reached):

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Signature, minutes preparer: /S/

Concurrence Chair: /S/

Attachments/Handouts

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogen
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: 26 June 1998

TO: Douglas C. Kriesel, Ph.D., Director
Worldwide Regulatory Affairs

ADDRESS: Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660
Phone (203) 284-6883
Fax (203) 284-7630

FROM: Brenda J. Atkins, Project Manager

IND: [redacted]

SUBJECT: **List of Quinolone Class Safety Issues**

As discussed during the June 24, 1998, teleconference, we are sending you the following list of quinolone class safety issues.

1. hypoglycemia
2. Temafloxacin syndrome
3. pancreatitis
4. phototoxicity
5. cardiotoxicity
6. tendonitis
7. rhabdomyolysis
8. crystalluria
9. hepatotoxicity

In preparing your safety reports for the NDA submission, please include a discussion of these specific events within each pivotal study submitted for specific indications as well as in the overall integrated safety summary.

We are providing the above comments via facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me on (301) 827-2127 if you have any questions regarding the contents of this transmission or if a teleconference is needed.

/S/

Brenda J. Atkins, B.S.
Project Manager
Division of Special Pathogen and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

Atkins 590

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Record of Teleconference

Date of Teleconference: December 18, 1998

IND: [redacted]

Drug: Gatifloxacin

Sponsor/Applicant: Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute

Indication: Nosocomial pneumonia

Subject: Clinical Pharmacology and Biopharmaceutics Reviewer comments on draft protocols AI420-061 and AI420-062

FDA Attendees, Titles, and Offices:
Funmilayo Ajayi, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Philip Colangelo, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Kathleen Uhl, M.D., Clinical Pharmacologist
Brenda J. Atkins, B.S., Project Manager

External Constituents and Titles:
Dennis Grasela, Pharm.D., Ph.D., Associate Director, Clinical Pharmacology
Claude Nicaise, M.D., Executive Director, Infectious Disease Clinical Research
Barry Fox, M.D., Infectious Diseases Clinical Research
Douglas C. Kriesel, Ph.D., Director, Worldwide Regulatory Affairs

Related Documents: Submissions 108 and 131, FDA facsimile of December 16, 1998

Objectives/Issues: Submission 131, dated November 16, 1998, received November 17, 1998, contained two draft protocols entitled, "**AI420-061**: A Randomized, Double-Blind, Multicenter, Comparative Phase III Study of **Gatifloxacin Versus Trovafloxacin in the Treatment of Nosocomial Pneumonia,**" and "**AI420-062**: An Open Label, Multicenter, Non-Comparative Phase III Study of **Gatifloxacin in the Treatment of Nosocomial Ventilator-Associated Pneumonia.**" Requests for clarification and additional information were provided to BMS via facsimile December 16, 1998. The purpose of this teleconference was for BMS to respond to the FDA comments listed in the December 16, 1998, facsimile. [The requests are duplicated below; information provided by BMS during the teleconference appears in italics.]

Discussion/Topics:

1. With regard to the evaluation of the Safety Data (Section 2.0, Attachment 3), the FDA agrees with you that the incidence of gatifloxacin related adverse events appears to be independent of the magnitude of observed Cmax and estimated AUC values generated in the Phase II and Phase III protocols noted. However, we would appreciate comment with regard to whether there is any relationship between the severity of drug-related adverse events and these PK parameters in these same protocols.

BMS stated that there were not enough subjects experiencing any one specific adverse event (AE) while taking gatifloxacin to obtain a good relationship with AUC and/or Cmax values. This was done for subjects enrolled in the bronchitis protocol and no discernable relationship with severity of AEs and Cmax values were detected.

2. With regard to the evaluation of the Safety Data (Section 2.0, Attachment 3), please provide the basis for stating that peak gatifloxacin concentrations (i.e. Cmax) need to be maintained above 3.5 mcg/mL.

   This was based on the MIC 90 for strep pneumo of 0.5mcg/mL. The Cmax to MIC ratio of 3.5 ÷ 0.5 is 7 and thus, the sponsor's theorectical basis for maintaining Cmax of 3.5 and above is to assure that Cmax/MIC ratios are at least 7 or greater.

3. With regard to the pharmacokinetic evaluation (Section 3.0, Attachment 3), there is concern that the simulations of the model predicted AUC at steady-state vs. estimated CLcr may not provide accurate estimates of the parameter values, particularly at CLcr 30 mL/min and less at the dose of 400 mg Q24 hrs. This concern is based upon the apparent discrepancy between the AUC values generated from the [redacted] PK study in renal impairment subjects, and particularly the mean AUC values in the subjects with severe impairment (including those undergoing hemodialysis or CAPD) and the predicted AUCss values at CLcr from 30 mL/min and under. The PK model used to simulate the AUC values at steady-state dosing of 400 mg Q24 hrs appears to under-predict the AUC when compared to those that were actually determined from a single 400 mg dose administration to the severe impairment group in the [redacted] PK study.

   Please provide any further comments with regard to this apparent discrepancy in the parameter estimates.

   The results provided in submission 131, attachment 3, were a preliminary fit of just the mean concentration data that was performed by an outside contractor. Recently this outside contractor has performed a fully integrated model fit of each individual subjects' concentration data. According to the sponsor, this model predicts AUC estimates with greater accuracy, i.e., as compared to the AUC's generated in [redacted] PK study. The sponsor is planning to submit results of the full model fits in the NDA. When asked if simulation was performed at the 600 mg dose, BMS responded with the reply that they did not.

4. To assist the FDA in evaluating the results of the simulations more adequately, it would be helpful if you could provide a tabulation of the predicted ranges of Cmaxss and AUCss values over the associated CLcr ranges for each of the various dosage regimen scenarios.

   BMS agreed to provide this information.

5. The specific instructions for dosing in patients undergoing hemodialysis or CAPD were not provided in the revised changes to Protocol AI420-061, but they are provided in Protocol AI420-062. These instructions should also be provided in Protocol AI420-061.

BMS stated that instructions for dosing in patients undergoing hemodialysis or CAPD will be incorporated into the final version of Protocol AI420-061.

6. In Protocol AI420-062, the revised changes for dosing indicate that gatifloxacin is removed by hemodialysis, with 30% of the drug removed. However, in the [redacted] PK study, it was concluded that ~14% of the administered dose was removed by a 4 hour hemodialysis session and ~11% was removed by peritoneal dialysis over an 8-day period. Please revise both protocols to reflect such results, or provide the rationale for refuting these results from the [redacted] PK study.

BMS will revise protocols to reflect data.

The FDA representatives stated that it was okay to go ahead with the protocols as proposed, but would keep a critical eye on results of the population PK estimates obtained from these protocols. FDA will be looking at estimates of PK exposure for both severely impaired patients (CLcr <30 mL/min) as well as moderately impaired patients (Clcr <50-30 mL/min).

Action/Outcome:

1. BMS will submit the protocol amendment to investigators today (December 18), obtain [redacted] approval, and submit to the FDA the second half of January 1999.
2. Studies PK-007, 04 and 3738 will be sent to Dr. Colangelo on Monday, December 21, 1998.

HFD 590

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogen
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: 17 June 1999

TO: Douglas C. Kriesel, Ph.D., Director
Worldwide Regulatory Affairs

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Phone (203) 677-6883
Fax (203) 284-7630

FROM: Brenda J. Atkins, Regulatory Project Manager

NDA DRUG: 21-062 - TEQUIN™ (gatifloxacin IV)

SUBJECT: **Request for change in the proprietary name from "TEQUIN™ for Injection" to "TEQUIN™ Injection"**

Please refer to your original New Drug Application (NDA) submission for TEQUIN™ (gatifloxacin IV) dated December 28, 1998, and to my June 11, 1999, facsimile containing the CDER Labeling and Nomenclature Committee (LNC) Chair's decision on the acceptability of the drug name. We also refer to your facsimile dated June 17, 1999, with documentation supporting your request for the change in the proprietary name from "TEQUIN™ for Injection" to "TEQUIN™ Injection".

The LNC Chair, Dan Boring, Ph.D., and the chemist reviewer, John Smith, Ph.D., for this application are in agreement with your request to change our previous recommendation of the proprietary name from "TEQUIN™ for Injection" to "TEQUIN™ Injection".

We are providing this information via facsimile for your convenience. Please feel free to contact me on (301) 827-2127 if you have any questions regarding the contents of this transmission.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

FROM: Anthony G. Proakis, Ph.D., Pharmacologist, HFD-110 /S/

THROUGH: Raymond J. Lipicky, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110 /S/

TO: Joyce Korvock, M.D. Division of Special Pathogen and Immunologic Drug Products, HFD-590
Dolores Bernato, Project Manager, HFD-590

SUBJECT: TEQUIN™, Gatifloxacin

DATE RECEIVED: 12/10/99
DATE COMPLETED: 12/14/99

INTRODUCTION

Bristol-Myers Squibb Pharmaceutical Research Institute submitted to the Division of Special Pathogen and Immunologic Drug Products (HFD-590) a New Drug Application (NDA # 21,061) for gatifloxacin, an antibacterial.

The Division of Special Pathogen and Immunologic Drug Products is requesting that we evaluate the results of a non-clinical pharmacology study titled "Effects of gatifloxacin and other quinolones on HERG (IKr) currents" to determine if the actions by gatifloxacin on potassium currents are sufficient to lead to adverse cardiac effects (QT-interval prolongation and arrhythmia).

STUDY DESCRIPTION AND RESULTS

Effects of Gatifloxacin and Other Quinolones on HERG (Ikr) Currents

This study assess the effects of gatifloxacin on the cardiac delayed rectifier current (IKr) encoded by the potassium channel gene, HERG (human-ether-related-gene) and compares the activity of gatifloxacin on HERG with other quinolone antibacterials. Voltage clamp techniques were used to measure membrane currents in HERG-expressing cells. The effects of compounds on HERG were calculated by measuring drug-induced inhibition of tail currents, elicited at –70 mV following voltage steps to activate the HERG current. Gatifloxacin and other quinolone antibacterials (sparfloxacin, grepafloxacin, [redacted] and ciprofloxacin) were tested at bath concentrations of 10, 30, 100 and 300 uM (n=5/concentration).

Dose-dependent inhibition of HERG was observed with all the compounds tested (Table 1). The degrees of inhibition of HERG at the four concentrations of sparfloxacin were comparable to those seen with grepafloxacin. At comparable concentrations, the degree of HERG inhibition produced by gatifloxacin was less that that seen with [redacted] sparfloxacin and

grepafloxacin. A 35% to 40% inhibition of HERG was used to compare relative potencies (defined as the differences in drug concentrations eliciting equivalent effects) among the quinolone compounds. At this level of HERG inhibition, gatifloxacin is approximately 1/10 as potent and [redacted] is about 1/3 as potent than either sparfloxacin or grepafloxacin. Ciprofloxacin produced the lowest degree of inhibition at comparable concentrations.

Table 1. % Inhibition of HERG

Compound	Drug Concentration (uM)			
	10	30	100	300
Ciprofloxacin	5.1 ± 3.1	6.3 ± 2.3	11.1 ± 4.8	16.6 ± 6.1
Gatifloxacin	3.3 ± 1.5	8.6 ± 3.4	20.4 ± 6.0	36.6 ± 7.7
Sparfloxacin	15.2 ±6.0	40.3 ± 7.8	64.8 ± 4.2	86.8 ± 1.5
Grepafloxacin	16.9 ±3.7	35.3 ± 3.6	60.8 ± 3.4	79.5 ± 3.6

Values are the mean ± SEM derived from 5 determinations

SUMMARY AND CONCLUSIONS

Sparfloxacin and grepafloxacin have been reported to prolong cardiac repolarization in some patients[1,2]. Concentration-dependent lengthening of action potential duration has also been observed with these fluoroquinolone antibacterials[3]. Results described in the current study indicate that these same fluoroquinolones produce concentration-dependent blockade of potassium current (IKr), which, most likely, is the underlying basis for prolongation of action potential duration and QTc interval prolongation. The sponsor states that gatifloxacin is approximately 1/10 as potent as either grepafloxacin or sparfloxacin and concludes that, at expected plasma concentrations [redacted] in humans, gatifloxacin would be unlikely to prolong the QT interval.

There are factors, other than this singular study, that must be considered before ruling out any cardiovascular liability for gatifloxacin. It should be emphasized that the potency differences between gatifloxacin and the other 2 fluoroquinolones on HERG/IKr inhibition are quantitative and not qualitative in nature. Thus, gatifloxacin is not totally devoid of this potassium channel blocking property. Further, the 10-fold difference in relative potency between gatifloxacin and the most serious fluoroquinolones were revealed under *in vitro* conditions. This relative potency separation is only meaningful if a similar separation exists under *in vivo* conditions (e.g. QT interval prolongation in animal models). Other factors for consideration include whether differences in bioavailability or antibacterial potency may diminish the apparent separation in potassium channel blockade seen between gatifloxacin and the other related fluoroquinolones.

If the relative potency of gatifloxacin in other test systems (e.g., action potential duration in canine Purkinje fibers, QTc-interval prolongation in dogs) shows a suitable degree of separation at equieffective concentrations of sparfloxacin or grepafloxacin, then the case for a lack of proarrhythmic potential becomes stronger. In the absence of confirmatory data, is it inappropriate to conclude that gatifloxacin is incapable of inducing serious arrhythmias in susceptible patients (congenital long QT syndrome or other predisposing factors).

REFERENCES

1. Lipsky BA, Dorr MB, Magner DJ, Talbot GH. Safety profile of sparfloxacin, a new fluoroquinolone antibiotic. CLIN THER, 1999 21 (1) 148-59.

2. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. CLIN INFECT DIS, 1999 28(2) 352-64.

3. Adamantidis MM, Dumotier BM, Caron JF, Bordet R. Sparfloxacin but not levofloxacin or ofloxacin prolong cardiac repolarization in rabbit Purkinje fibers. FUNDAM CLIN PHARMACOL, 1998 12(1) 70-76.

HFD-590/ Div. Files
HFD-110
HFD-110/CResnick
HFD-110/JKoerner

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogen
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: December 27, 1999

TO: Robert Kessler
Worldwide Regulatory Affairs

ADDRESS: Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
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Phone (203) 677-6883
Fax (203) 284-7630

FROM: Leo Chan, Regulatory Project Manager for
Laurie Bernato, Regulatory Project Manager

IND: [redacted]

Drug: TEQUIN™ (gatifloxacin)

SUBJECT: Pediatric Studies

Please refer to your initial submission to [redacted] dated December 21,1998, containing protocol AI420-074 entitled, "Non-randomized, Open-Label, Parallel Group, Single-Dose, Dose-Escalation Study of the Pharmacokinetics and Safety of Orally Administered Gatifloxacin in Hospitalized Pediatric Patients", and to submission 005 dated June 1, 1999, containing protocol AI420-075 entitled, "Open-Label, Non-Randomized Study of the Middle Ear Fluid Penetration of Gatifloxacin in Children Undergoing Tympanostomy Tube Placement." Refer also to [redacted] dated November 15, 1999, containing protocol AI420-054 entitled "Non-Randomized, Open-Label, Parallel Group, Single-Dose, Dose-Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Intravenously Administered Gatifloxacin in Pediatric Patients."

Please refer also to our teleconference on December 1, 1999.

At our teleconference on December 1, 1999, you stated your intention not to initiate these three protocols as submitted until after our scheduled meeting in January. We will consider these to be draft protocols in order to allow for the opportunity of further discussion. We have scheduled a meeting on January 5, 2000 from 1- 3 PM for this discussion and to afford you the opportunity to present any additional data supporting their safe initiation.

Please note that the protocols should be resubmitted prior to initiation.

We are providing this information via facsimile for your convenience. Please feel free to contact me on (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Leo Chan, R.Ph., Regulatory Project Manager for
D. Laurie Bernato, R.N., MN
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21062/000**
Priority: **1S**
Org Code: **590**
Stamp: **28-DEC-1998** Regulatory Due: **28-OCT-1999**
Action Goal:
District Goal: **29-AUG-1999**
Applicant: **BRISTOL MYERS SQUIBB**
5 RESEARCH PKY
WALLINGFORD, CT 064927660
Brand Name: **TEQUIN (GATIFLOXACIN) 200 MG/400MG IV**
Established Name:
Generic Name: **GATIFLOXACIN**
Dosage Form: **INJ (INJECTION)**
Strength: **2 MG/ML & 10 MG/ML**

FDA Contacts:
B. ATKINS (HFD-590) 301-827-2127 , Project Manager
J. SMITH (HFD-590) 301-827-2175 , Review Chemist
N. SCHMUFF (HFD-590) 301-827-2425 , Team Leader

Overall Recommendation:

ACCEPTABLE on 04-NOV-1999 by S. ADAMS (HFD-320) 301-594-0095

Establishment:
DMF No:
AADA No:

Profile: **LVP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
FIRM RESPONSE TO DEFIC. ADEQ

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER
FINISHED DOSAGE STERILIZER

Establishment: **2627673**
BRISTOL LABORATORIES INC DIV B
FOREIGN TRADE ZONE #7 RD #114
MAYAGUEZ, PR 00680
DMF No:
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER
FINISHED DOSAGE STERILIZER

Establishment: **2211101**
BRISTOL MYERS SQUIBB CO
1 SQUIBB DR
DMF No:
AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

NEW BRUNSWICK, NJ 08903

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment: **9611256**
KYORIN PHARMACEUTICAL CO LT
14-3 KOHAN 1-CHOME
OKAYA (NAGANO) 394, , JA
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

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45 DAY MEETING CHECKLIST

NDA Number: 21-061 **Applicant:** Bristol-Myers Squibb **Stamp Date:** 12/29/98
Drug Name: TEQUIN™ (gatifloxacin) Tablets, 200-mg & 400-mg
IS THE CMC SECTION APPLICATION FILEABLE? (Yes or no) YES
The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	YES	NO
1.	On its face, is the section organized adequately?	X	
2.	Is the section indexed and paginated adequately?	X	
3.	On its face, is the section legible?	X	
4.	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X	
5.	Is a statement provided that all facilities are ready for GMP inspection?	X	
6.	Has a environmental assessment report been provided?	X	
7.	Does the section contain appropriate controls for the drug substance?	X	
8.	Does the section contain appropriate controls for the product?	X	
9.	Has stability data been provided to support the requested expiration date?	X	
10.	Has all information requested at pre-NDA meetings been included?	X	
11.	Have draft labels and labeling been provided?	X	X*
12.	Has an investigational formulations section been provided?	X	

* Draft labeling, but not draft *labels*.

cc:
Orig. NDA
HFD-590/Division File
HFD-590/Chemist
HFD-590/CSO

/S/ 2/10/99
John Smith, Chemist, HFD-590

/S/ 2/10/99
Norman R. Schmuff, Chemistry Team Leader HFD-590

HFD 500 / Memo

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 21-061 and 21-062.
Name Of Drug: TEQUIN™ Tablets (gatifloxacin) and TEQUIN™ I.V. (gatifloxacin)
Applicant: Bristol-Myers Squibb Company
Submission Date: December 28, 1998

Indication(s): 7 total, 4 by this reviewer;
(1) community acquired pneumonia,
(2) acute exacerbation of chronic bronchitis,
(3) acute sinusitis,
(4) uncomplicated gonococcal urethritis/cervicitis (note: the medical officer will review this alone unless it is later determined that a statistical review is needed)

Number And Type Of Controlled Clinical Studies By Indication: 11 pivotal phase III studies, 7 assessed by this reviewer;
(1) community acquired pneumonia: 3 randomized, active-controlled, double-blind clinical trials,
(2) acute exacerbation of chronic bronchitis: 2 randomized, active-controlled, double-blind clinical trials,
(3) acute sinusitis: 1 randomized, active-controlled, double-blind clinical trial,
(4) uncomplicated gonococcal infection: 1 randomized, active-controlled, double-blind, clinical trial.

Statistical Reviewer: Karen Higgins
Clinical Reviewer: Joyce Korvick, Eric Mann, and Renata Albrecht (for the 4 indications above)
Project Manager: Brenda Atkins

45 Day Meeting Date: February 10, 1999
Promise Date: November 1, 1999
User Fee Date: December 28, 1999

I. ORGANIZATION AND DATA PRESENTATION	YES	NO	N/A
A. Is there a comprehensive table of contents with adequate indexing and pagination?	✔		
B. Are the original protocols, protocol amendments and proposed label provided?	✔		
C. Adverse event listings by center and time of occurrence relative to enrollment date.	✔		

		YES	NO	N/A
1.	Are adverse events from cited sources (foreign and domestic) provided?			✔
D.	Is a CANDA or an electronic submission of the data necessary?	✔		
E.	If the data have been submitted electronically, has adequate documentation of the data sets been provided?	✔		
F.	Are inclusion/exclusion (evaluability) criteria adequately coded and described:	✔		
G.	Are there discrepancies between CRF information and CANDA/Jacket data?			✔
H.	If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?	✔		
1.	If not, can you estimate the time required to correct problems?			✔

II. STATISTICAL METHODOLOGY		YES	NO	N/A
A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✔		
B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	✔		
1.	If subset analyses were not done, was an acceptable explanation of why given?			✔
C.	Based on the summary analyses of each study, do you believe:			

		YES	NO	N/A
1.	The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?	✔		

Note: The Analyses do not reflect the randomization used in the design. This will be addressed in the review.

2.	If there are multiplicity issues, has this been adequately addressed?			✔
3	Intent-to-treat (ITT) analyses are properly performed?	✔		
4.	Sufficient and appropriate references were included for novel statistical approaches?			✔
D.	If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?			✔
E.	Are there studies which are incomplete or ongoing?	✔		

Note: Study #AI420-007 is an open-label study of gatifloxacin in the treatment of acute, uncomplicated bacterial sinusitis which should be completed by 01 March 1999. Study #AI420-064 is a double-blind study of acute exacerbation of gatifloxacin versus clarithromycin in the treatment of chronic bronchitis which should be completed by 30 June 1999. Study #AI420-067 is a double-blind study of gatifloxacin versus oral trovafloxacin in the treatment of community-acquired pneumonia which should be completed by 11 June 1999. None of these studies are included in the seven pivotal studies mentioned above.

F.	Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?	✔		
1.	Is there anything significant yet regarding safety or AE evaluations?		✔	

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Yes.

/S/ 2/11/99

Karen Higgins, Sc.D.
Mathematical Statistician, DOB III

Concur: /S/ 2/11/99
Nancy Silliman, Ph.D.
Statistical Teamleader, DOB III

cc:
Archival: NDA #21-061 and NDA #21-062
HFD-590
HFD-590/Dr. Goldberger
HFD-590/Dr. Cavaille Coll
HFD-590/Dr. Korvick
HFD-520/Dr. Mann
HFD-590/Dr. Roca
HFD-590/Dr. Tiernan
HFD-590/Dr. Albrecht
HFD-590/Ms. ~~Atkins~~ Bernato
HFD-725/Dr. Huque
HFD-725/Dr. Silliman
HFD-725/Dr. Higgins
HFD-725/Ms. Shores

HFD-5[illegible]/Mr. Bernal

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDAs:	21-061 and 21-062
Name Of Drug:	TEQUIN™ Tablets and TEQUIN™ I.V. (gatifloxacin)
Applicant:	Bristol-Myers Squibb Company
Submission Date:	December 28, 1998
Indication(s):	7 total, 3 by this reviewer: (1) complicated urinary tract infection, (2) uncomplicated urinary tract infection, (3) uncomplicated skin and skin structure infections
Number And Type Of Controlled Clinical Studies By Indication:	11 pivotal phase III studies, 4 assessed by this reviewer: (1) complicated urinary tract infection: 2 randomized, active-controlled, double-blind clinical trials, (2) uncomplicated urinary tract infection: 1 randomized, active-controlled, double-blind clinical trial, (3) uncomplicated skin and skin structure infections: 1 randomized, active-controlled, double-blind clinical trial
Statistical Reviewer:	Nancy Silliman, Ph.D.
Clinical Reviewer:	Rose Tiernan, M.D., and Rigo Roca, M.D. (for the 3 indications above)
Project Manager:	Brenda Atkins
45 Day Meeting Date:	February 22, 1999
Review Goal Date:	November 1, 1999
User Fee Date:	December 28, 1999

I. ORGANIZATION AND DATA PRESENTATION		YES	NO	N/A
A.	Is there a comprehensive table of contents with adequate indexing and pagination?	✔		
B.	Are the original protocols, protocol amendments and proposed label provided?	✔		
C.	Adverse event listings by center and time of occurrence relative to enrollment date.	✔		
1.	Are adverse events from cited sources (foreign and domestic) provided?	✔		

		YES	NO	N/A
D.	Is a CANDA or an electronic submission of the data necessary?	✔		
E.	If the data have been submitted electronically, has adequate documentation of the data sets been provided?	✔		
F.	Are inclusion/exclusion (evaluability) criteria adequately coded and described:	✔		
G.	Are there discrepancies between CRF information and CANDA/Jacket data?			✔
H.	If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?	✔		
1.	If not, can you estimate the time required to correct problems?			✔

II. STATISTICAL METHODOLOGY		YES	NO	N/A
A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✔		
B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	✔		
1.	If subset analyses were not done, was an acceptable explanation of why given?			✔

		YES	NO	N/A
C.	Based on the summary analyses of each study, do you believe:			
1.	The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?	✔		
	Note: Analyses performed by the sponsor do not reflect the dynamic randomization used in the design. This will be addressed in the review.			
2.	If there are multiplicity issues, has this been adequately addressed?	✔		
3	Intent-to-treat (ITT) analyses are properly performed?	✔		
4.	Sufficient and appropriate references were included for novel statistical approaches?			✔
D.	If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?			✔
E.	Are there studies which are incomplete or ongoing?		✔	
F.	Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?	✔		
1.	Is there anything significant yet regarding safety or AE evaluations?		✔	

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Yes.

/S/ 2/10/99

Nancy Silliman, Ph.D.
Statistical Teamleader, DB III

Concur: /S/ 2/11/99
Mohammad Huque, Ph.D.
Director, DB III

cc:
Archival: NDA #21-061 and NDA #21-062
HFD-590
HFD-590/Dr. Goldberger
HFD-590/Dr. Cavaille-Coll
HFD-590/Dr. Korvick
HFD-520/Dr. Mann
HFD-590/Dr. Roca
HFD-590/Dr. Tiernan
HFD-590/Dr. Albrecht
HFD-590/Ms. ~~Atkins~~ Bernata
HFD-725/Dr. Huque
HFD-725/Dr. Silliman
HFD-725/Dr. Higgins
HFD-725/Ms. Shores

NDAs: 21061 (oral) (Tequin) Gatifloxacin HFD-590/Bernato
21062 (IV)

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:	YES	NO
PHARMACOLOGY:		
(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin?	✓	
(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review begin?	✓	
(3) On its face, is the pharmacology section of the NDA legible so that substantive review can begin?	✓	
(4) Are all required(*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	✓	
(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required?	✓	
(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	mg/kg comparisons should be removed as PK exposure data are available	
(7) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	✓	

	Yes	No
(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	✓	
(9) Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	✓	
(10) Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	conduct of animal studies appears to have been reasonable	
(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	✓	

/S/ 2/19/99
Reviewing Pharmacology Officer

/S/ 2/19/99
Supervisory Pharmacology Officer

cc: Archival NDA 21-061
NDA 21-062
HFD-590/BERNATO/RPM

HFD-590 / L Bernal

① Uncomplicated Skin & Skin Structure Infections

② Complicated Urinary Tract Infections.

45-DAY MEETING
Fileability Checklist
NDA 21061 (S-00)
— CLINICAL —

Based on your initial overview of the NDA application:

		YES (✓)	NO (✓)
1)	On its face, is the clinical section of the NDA organized in a manner to allow a substantive review to begin? (See 21 CFR §314.50(d)(5).)	☑	☐
2)	Is the clinical section of the NDA indexed and paginated in a manner to allow a substantive review to begin? (See 21 CFR §314.50.)	☑	☐
3)	On its face, is the clinical section of the NDA legible so that a substantive review can begin?	☑	☐
4)	If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	☑	☐
5)	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	☑	☐
6)	Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	☑	☐
7)	Are all data sets for pivotal efficacy studies complete for all indications requested?	☐	☐
8)	Do all pivotal efficacy studies appear to be adequate and well controlled within current FDA (see 21 CFR §314.126) and divisional/office policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	☑	☐
9)	Has the applicant submitted case report tabulations (CRT; line listings and patient profiles) in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in a format agreed to previously by the Division? If the CRTs were submitted electronically, are they consistent with CDER's *Guidance for Industry - Archiving Submissions for Electronic Format — NDAs*?	☑	☐
10)	Has the applicant submitted a rationale for assuming the applicability of foreign data (disease specific) to the US population?	☐	☐ NA

11) Has the applicant submitted all additional required case report forms (CRF) (beyond deaths and dropouts) previously requested by the Division? ☑ ☐

12) If CRFs were submitted electronically, are they consistent with CDER's *Guidance for Industry - Archiving Submissions for Electronic Format — NDAs*? ☑ ☐

13) Has the applicant presented safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?

13) Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? ☑ ☐

14) Has the applicant submitted draft labeling consistent with 21 CFR §201.56 and §201.57, current divisional/office policies, and the design of the development package? ☑ ☐

15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? ☑ ☐

16) From a clinical perspective, is this NDA fileable? If "no", please state why it is not. (Use additional sheet of paper if needed.) ☑ ☐ _____

.....

If certain claims are not fileable, please state which claims they are and why they are not fileable. (Use additional sheet of paper if needed.) _____

/S/ 2/22/99
Reviewing Medical Officer (sign & date)

/S/ 2/22/99
Medical Team Leader (sign & date)

cc: ARCHIVAL NDA 21-061
NDA 21-062
HFD-590/LBERNATO/RPM

HFD 590/Lbarrato

Teguin

45-DAY MEETING
Fileability Checklist
NDA 21064 (S-002)

SINUSITIS INDICATION — CLINICAL —

Based on your initial overview of the NDA application:

	YES (✓)	NO (✓)
1) On its face, is the clinical section of the NDA organized in a manner to allow a substantive review to begin? (See 21 CFR §314.50(d)(5).)	☒	☐
2) Is the clinical section of the NDA indexed and paginated in a manner to allow a substantive review to begin? (See 21 CFR §314.50.)	☒	☐
3) On its face, is the clinical section of the NDA legible so that a substantive review can begin?	☒	☐
4) If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	☐	☐
5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	☒	☐
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	☒	☐
7) Are all data sets for pivotal efficacy studies complete for all indications requested? (Open label bacteriology study ongoing)	☐	☒ (?)
8) Do all pivotal efficacy studies appear to be adequate and well controlled within current FDA (see 21 CFR §314.126) and divisional/office policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	☒	☐
9) Has the applicant submitted case report tabulations (CRT; line listings and patient profiles) in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in a format agreed to previously by the Division? If the CRTs were submitted electronically, are they consistent with CDER's *Guidance for Industry - Archiving Submissions for Electronic Format — NDAs*?	☒	☐
10) Has the applicant submitted a rationale for assuming the applicability of foreign data (disease specific) to the US population?	☐	☐

11) Has the applicant submitted all additional required case report forms (CRF) (beyond deaths and dropouts) previously requested by the Division? ☒ ☐

12) If CRFs were submitted electronically, are they consistent with CDER's *Guidance for Industry - Archiving Submissions for Electronic Format — NDAs*? ☒ ☐

13) Has the applicant presented safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? ☒

13) Has the applicant presented a safety assessment based on <u>all</u> current worldwide knowledge regarding this product? ☐ ☐

14) Has the applicant submitted draft labeling consistent with 21 CFR §201.56 and §201.57, current divisional/office policies, and the design of the development package? ☒ ☐

15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? ☒ ☐

16) From a clinical perspective, is this NDA fileable? If "no", please state why it is not. (Use additional sheet of paper if needed.) ☒ ☐

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If certain claims are not fileable, please state which claims they are and why they are not fileable. (Use additional sheet of paper if needed.) _____

_____

_____

_____

_____

/S/ 2/22/99

Reviewing Medical Officer (sign & date)

/S/ 2/23/99

Medical Team Leader (sign & date)

cc: ARCHIVAL NDA 21-061
NDA 21-062
HFD-590/BERNATO/RPM

HFD590/Reynolds

45-DAY MEETING
Fileability Checklist
NDA 21-061 (S-___)
— CLINICAL —
21-062

Based on your initial overview of the NDA application:	YES (✓)	NO (✓)
1) On its face, is the clinical section of the NDA organized in a manner to allow a substantive review to begin? (See 21 CFR §314.50(d)(5).)	☑	☐
2) Is the clinical section of the NDA indexed and paginated in a manner to allow a substantive review to begin? (See 21 CFR §314.50.)	☑	☐
3) On its face, is the clinical section of the NDA legible so that a substantive review can begin?	☑	☐
4) If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	☑	☐
5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	☑	☐
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	☑	☐
7) Are all data sets for pivotal efficacy studies complete for all indications requested?	☑	☐
8) Do all pivotal efficacy studies appear to be adequate and well controlled within current FDA (see 21 CFR §314.126) and divisional/office policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	☑	☐
9) Has the applicant submitted case report tabulations (CRT; line listings and patient profiles) in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in a format agreed to previously by the Division? If the CRTs were submitted electronically, are they consistent with CDER's *Guidance for Industry - Archiving Submissions for Electronic Format — NDAs*?	☑ 2	☐
10) Has the applicant submitted a rationale for assuming the applicability of foreign data (disease specific) to the US population?	☐	☑ NA

11) Has the applicant submitted all additional required case report forms (CRF) (beyond deaths and dropouts) previously requested by the Division? ☑ ☐

12) If CRFs were submitted electronically, are they consistent with CDER's *Guidance for Industry - Archiving Submissions for Electronic Format — NDAs*? ☐ ☐ 2.

13) Has the applicant presented safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? ☑

13) Has the applicant presented a safety assessment based on <u>all</u> current worldwide knowledge regarding this product? ☐ ☐ 2.

14) Has the applicant submitted draft labeling consistent with 21 CFR §201.56 and §201.57, current divisional/office policies, and the design of the development package? ☑ ☐

15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? ☐ ☐

16) From a clinical perspective, is this NDA fileable? If "no", please state why it is not. (Use additional sheet of paper if needed.) _____ ☑ ☐

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If certain claims are not fileable, please state which claims they are and why they are not fileable. (Use additional sheet of paper if needed.) _____

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/S/ , 2/19/99

Reviewing Medical Officer (sign & date)

cc: Archival NDA 21-061
NDA 21-062
HFD-590/Bernato/RPM

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Medical Team Leader (sign & date)

HFD-590 / Evaluate

45 DAY MEETING CHECKLIST

F. CABILITY:

On initial overview of the NDA application: YES NO

MICROBIOLOGY:

(1) On its face, is the microbiologic section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin ✓

(3) On its face, is the microbiologic section of the NDA legible so that substantive review can begin? ✓

(4) On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains, and using necessary numbers of approved laboratories to meet current divisional standard for approvability of the submitted draft labeling? ✓

(5) Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling? N/A

(6) Has the applicant submitted draft breakpoint and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin? ✓

(7) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? N/A

(8) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policy, and the design of the development package? ✓

	Yes	NO
(9) If necessary for this product, has the applicant submitted the sterilization procedures and documentation required for approval of the manufacturing and controls elements of this NDA?	N/A	
(9) From a microbiology perspective, is this NDA fileable? If "no", please state on reverse why it is not.	✓	

APPEARS THIS WAY
ON ORIGINAL

/S/

Reviewing Microbiology Officer

/S/

Supervisory Microbiology Officer

cc: Archival NDA 21-061
NDA 21-062
HFD-590/BERNATO/RPM

HFD-590/Bernato

45 DAY MEETING CHECKLIST

FILEABILITY:

NDA 21-061
NDA 21-062

On initial overview of the NDA application: YES NO

BIOPHARMACEUTICAL:

(1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓

(3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? ✓

(4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic pharmacokinetic characterization requirements for approvability of this product? ✓

(5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparisons of and establish the equivalence of the product to be marketed and the product(s) used in the clinical development? ✓

(6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? ✓

cc: Archival NDA 21-061
NDA 21-062
HFD-590/BERNATO/RPM

/S/ 1/22/99
Reviewing Biopharmaceutics Officer

/S/ 1/22/99
Supervisory Biopharmaceutics Officer