CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-554

Administrative/Correspondence Reviews

Section 14 – Patent Certification

All investigations relied upon by Bayer Corporation in this NDA were conducted by or for Bayer using drug substance and drug product in accordance with the patents listed in the Patent Information Section.

Please refer to Section 13, Patent Information.

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

Patent Number:	4,670,444
Expiration Date:	December 9, 2003
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Corporation), residing in the U.S.

The undersigned declares that the U.S. Patent Number 4,670,444 covers the formulation, composition and method of use of ciprofloxacin. This product is the subject of this application for which approval is being sought.

Mary E. Taylor, MPH
Vice President, Regulatory Affairs
Bayer Corporation

EXCLUSIVITY SUMMARY for NDA # 21-554 SUPPL #
Trade Name CIPRO® XR Generic Name ciprofloxacin extended release tablets
Applicant Name Bayer Pharmaceuticals Corporation HFD- 590

Approval Date August 28, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/____/ NO /_X__/

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

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

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

      YES /_X__/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /___/NO /_X_ /

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

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

YES /___/ NO /_X__/

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

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

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_X__/

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

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

1. Single active ingredient product.

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

YES /X___/ NO /___/

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

NDA # 19-537	Cipro® tablets
NDA # 20-780	Cipro® oral suspension
NDA # 19-847, 19-857, 19-858	Cipro® I.V.
NDA # 21-473	Cipro® XR

2. Combination product.

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

YES /___/NO/___/N/A_X_

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

NDA #

NDA #

NDA #

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

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

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

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

YES /__X_/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

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

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

YES /___/ NO /_X__/

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

YES /___/ NO /X__/

If yes, explain:

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

YES /___/ NO /__X_/

If yes, explain:

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

Investigation #1, Study # ___100275

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

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

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

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #_1_, Study # ___100275

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1

IND # 61,331 YES /_X_/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

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

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

Jouhayna S. Saliba, Pharm.D.
Signature of Preparer
Title: Regulatory Health Project Manager

Renata Albrecht, M.D.
Signature of Division Director

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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

/s/

Jouhayna Saliba
12/17/03 10:57:37 AM

Renata Albrecht
12/17/03 04:42:31 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-554 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: October 29, 2002 Action Date: August 28, 2003

HFD-590 Trade and generic names/dosage form: CIPRO® XR (ciprofloxacin extended release tablets)

Applicant: Bayer Pharmaceuticals Corporation Therapeutic Class: quinolone

Indication(s) previously approved: Uncomplicated urinary tract infection

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

Number of indications for this application(s): 2

Indication #1: Complicated urinary tract infection

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

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ___Partial Waiver __X__Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred: 0-16 years

Min _____	**kg**_____	**mo.**_____	**yr.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**Tanner Stage**_____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____

Jouhayna S. Saliba, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Acute Uncomplicated pyelonephritis

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

☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply: ___Partial Waiver __X__Deferred ___Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:0-16 years

Min ____	**kg____**	**mo.____**	**yr._0__**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr._16_**	**Tanner Stage____**

Reason(s) for deferral:

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

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jouhayna S. Saliba, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Jouhayna Saliba
10/17/03 02:31:54 PM

Section 16 : Debarment Certification

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

Mary E. Taylor, MPH
Vice President, North America Regulatory Affairs
Bayer Corporation

DESK COPY

Bayer HealthCare
Pharmaceuticals

August 28, 2003

Renata Albrecht, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-554
CIPRO® XR (ciprofloxacin extended-release tablets) 1000 mg
Response to FDA Request for Information
Phase IV Commitments

Bayer Pharmaceuticals
Corporation
400 Morgan Lane
West Haven, CT 06516

Tel. 203 812-2000
www.bayer.com

Dear Dr. Albrecht,

Reference is made to the Cipro XR NDA, 21-554, currently under review by the Division. As proposed in recent discussions and correspondence between Bayer and the Division, Bayer Pharmaceuticals Corporation agrees to the following Phase IV commitments as a condition of approval for this NDA:

1. Provide confirmative evidence of CIPRO XR efficacy in treating complicated urinary tract infections caused by *P. aeruginosa*.

- Protocol submission by no later than six months from date of approval.
- Study start by no later than twelve months from the date of approval.
- Final report submitted by no later than thirty-nine months from the date of approval.

2. Perform Monte Carlo simulations to obtain steady state estimates of ciprofloxacin systemic exposure after administration of the following regimens. These simulations are to be performed over the ranges of creatinine clearance (CLcr) values specified below for normal renal function and mild, moderate, and severe renal impairment, rather than using a single CLcr value:

- 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CLcr 50-80mL/min)
- 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CLcr 30-50 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CLcr <30 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CLcr 50-80 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CLcr 30-50 mL/min)
- 750 mg CIPRO® IR bid for 14 days in patients with normal renal function (CLcr 81-120 mL/min)

Final Report Submission: Within 12 months from the date of approval

If any questions or concerns arise from this information, do not hesitate to contact me at (203) 812-5172 or at andrew.verderame.b@bayer.com.

Sincerely,

Andrew S. Verderame
Director, Regulatory Affairs

Desk copy : Jouhayna Saliba, PharmD, Project Manager

8/28/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-554	Efficacy Supplement Type SE-	Supplement Number	
Drug: **CIPRO® XR**		Applicant: **Bayer Pharmaceutical Corporation**	
RPM: **Jouhayna Saliba, Pharm.D.**		**HFD-590**	Phone # 301-827-2127
Application Type: **(X)** 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**August 29, 2003**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	**(X)** Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	**(X)** Verified
❖ Patent	
• Information: Verify that patent information was submitted	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	**X**
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**X**
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**N/A**
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes **(X)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**N/A**
• Most recent applicant-proposed labeling	**X**
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**X**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**X**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**X**
• Reviews	**See CMC review**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**N/A**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**X**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**X**
❖ Memoranda and Telecons	**N/A**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A**
• Pre-NDA meeting (indicate date)	**N/A**
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other	**N/A**

Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	**N/A**
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**N/A**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**September 5, 2003**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**April 24, 2003**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**N/A**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**X**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**July 28, 2003**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**September 15, 2003**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**August 30, 2003**
❖ Environmental Assessment – **See CMC review**	
• Categorical Exclusion *(indicate review date)*	**August 30, 2003**
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**N/A**
❖ Facilities inspection (provide EER report) **See CMC review**	Date completed: **December 17, 2002** (**X**) Acceptable ( ) Withhold recommendation
❖ Methods validation – **Not completed at time of review**	( ) Completed (**X**) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**March 29, 2003**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**

'02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bayer Pharmaceuticals Corporation	August 28, 2003
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(203) 812-5172	(203) 812-5029
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 400 Morgan Lane, West Haven, CT 06516	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-554

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
ciprofloxacin extended-release tablets	Cipro® XR

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*): 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride, monohydrate

CODE NAME (*If any*): BAY o 9867 and BAY q 3939

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Extended-Release Tablets	1000 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis

APPLICATION INFORMATION

PLICATION TYPE
k one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA Request for Information-Revised Phase IV Commitments

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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

#21,804	NDA #19-537	DMF	DMF	DMF	
#25,173	NDA #19-847	DMF	DMF	DMF	
IND #43,007	NDA #19-857	DMF	DMF	DMF	
IND #61,331	NDA #20-780	DMF	DMF	DMF	
		DMF	DMF		

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER *(Specify)* Response to FDA Request for Information-Revised Phase IV Commitments

CERTIFICATION

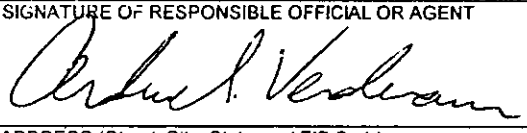
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

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

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Andrew S. Verderame Director, Regulatory Affairs	8/28/03

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
400 Morgan Lane West Haven, CT 06516	(203) 812-5172

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

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

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

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 21-554
Trade Name: Cipro® XR
Generic Name: Ciprofloxacin / Ciprofloxacin HCL
Strength: 1000mg tablets

Applicant: Bayer Pharmaceutical Corporation

Date of Application: October 29, 2002
Date of Receipt: October 29, 2002
Date of Filing Meeting: December 9, 2002
Filing Date: December 29, 2002

Indications requested: Complicated UTI and acute uncomplicated pyelonephritis

Type of Application: Full NDA _X_____ Supplement _____
(b)(1) ____X___ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S___X___ P_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.) 3____
Other (orphan, OTC, etc.)_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES X NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain. N/A

User Fee Status: Paid ____X____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES__X____ NO_____
User Fee ID# 4407___
Clinical data? YES ___X____ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: **August 29, 2003**

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? X YES NO
- Form 356h included with authorized signature? X YES NO

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? **X** YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? **X** YES NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO **X** NA

- Patent information included with authorized signature? **X** YES NO

- Exclusivity requested? YES; If yes, _____years **X** NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? **X** YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? **X** YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES **X** NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:
  Waiver requested for all ages of pediatric population
- Field Copy Certification (that it is a true copy of the CMC technical section)? **X** YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? **X** YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: **61,331**

End-of-Phase 2 Meeting? **X** NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? **X** NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? **X** YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
X YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO **X** N/A

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO **X** N/A

Advisory Committee Meeting needed? YES, date if known _____ **X** NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO **X** N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? **X** YES NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? **X** YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? **N/A**

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO
If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 9, 2002

BACKGROUND
Cipro XR, 500mg, was approved for uncomplicated UTI and this NDA was submitted requesting two indications, complicated UTI and acute uncomplicated pyelonephritis. The strength of the tablets are 1000mg.

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Joette Meyer
Statistical:	Ruthanna Davi
Pharmacology/Toxicology:	Stephen Hundley
Chemist:	Dorota Matecka
Environmental Assessment (if needed):	
Biopharmaceutical:	Dakshina Chilukuri
Microbiology, clinical (for antimicrobial products only):	Pete Dionne
Project Manager:	Jouhayna Saliba

Per reviewers, all parts in English, or English translation? YES_X____ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO___ X _____

MICROBIOLOGY CLINICAL – File_____ X _____ Refuse to file_____

STATISTICAL – File _____ X _____ Refuse to file _____

BIOPHARMACEUTICS – File ____ X _____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ____ X _____

PHARMACOLOGY – File ___ X _____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X___NO_____ File__ X ___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

____ X ___The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
_____ The application is unsuitable for filing. Explain why:

__Jouhayna Saliba_____
Regulatory Project Manager, HFD-590

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/s/

Jouhayna Saliba
10/17/03 03:32:13 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 17, 2003

To: Robin Christoforides	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** (301) 827-2387

Subject: Information requested and discussed a the July 10, 2003 teleconference
Additional requests that have come up after the teleconference

Total no. of pages including cover: 5

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-554
CIPRO® XR

Dear Ms. Christoforides:

As per our teleconference from July 10th, for the organisms that appear in the table in the clinical studies section for which there are less than 10 patients listed, please articulate what information is available to support your inclusion in this table. The type of information that would be helpful may include, but is not limited to, the following:

1. Whether the immediate-release formulation of ciprofloxacin has this organism listed for the indication(s) of complicated UTI and/or AUP.

2. Information to support extrapolation of ciprofloxacin immediate release formulation efficacy data to support efficacy of the XR formulation against the organisms in question.

3. Information regarding the pathophysiology of complicated UTI and/or AUP and ciprofloxacin that could be used to support the position that immediate-release formulation efficacy data can be used to extrapolate that ciprofloxacin XR would have similar efficacy against the organisms in question.

4. Information from the literature that would indicate whether or not a change has been noted in ciprofloxacin's efficacy against the organism in question since the immediate-release formulation became available, in the indication of complicated UTI/AUP."

Following are the discussion items and recommendations brought up at the teleconference regarding the Monte Carlo report:

1. It appears that the FO method was used in the modeling and simulation. It is known that FOCE/INTERACTION method is preferable for a relatively dense data set. Please address why only FO was used.

2. In the simulation, according to the code, CL_{cr} of 120 mL/min, 60 mL/min and 20mL/min were selected to represent healthy, moderate/mild renally impaired and severely renal impaired, respectively. This approach is considered to be inadequate. It is preferable to simulate with ranges of CL_{cr} values for normal renal function (80 to 120 mL/min), mild (51-79 mL/min), moderate (31-50 mL/min) and severe (10-30 mL/min) renal impairment. Therefore, as a Phase IV commitment, please perform additional Monte-Carlo simulations to obtain estimates of ciprofloxacin systemic exposure after administration of the following regimens:

   - 1000 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} —) mL/min)
   - 1000 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} – 50 mL/min)

- 500 mg CIPRO® XR for 14 days in patients with severe renal impairment (CL_{cr} <30 mL/min)
- 500 mg CIPRO® XR for 14 days in patients with mild renal impairment (CL_{cr} — —\ mL/min)
- 500 mg CIPRO® XR for 14 days in patients with moderate renal impairment (CL_{cr} — 50 mL/min)
- 750 mg CIPRO® IR bid for 14 days in patients with normal renal function (CL_{cr} — 120 mL/min)

3. The established relationship between clearance (CL) of intravenously administered ciprofloxacin and creatinine clearance (CL_{cr}) was used. However, we feel that it is more appropriate to develop a relationship using available renal impairment data following administration of the orally administered Cipro IR tablet and use it for the purpose of modeling and simulations. We recommend that you re-develop the relationship between oral ciprofloxacin clearance and creatinine clearance (CL_{cr}) and compare with the previous results.

In addition, we would like to provide the following comments and requests, which came up after the July 10, 2003 teleconference.

We note that there is a differential rate of exclusion from the Cipro XR and Cipro BID treatment arms in Study 100275. We also note that in your table which details the reasons for exclusion from the Per Protocol analysis, that patients may not be categorized by the major reason for exclusion. For example, a patient in the category "No valid TOC urine culture" may have been excluded due to a "ciprofloxacin resistant pathogen" and yet there is also a category called "organism resistant to study drug". Therefore, we would like you to reclassify patients based upon the root cause for exclusion. Examples of exclusion categories which are acceptable to use include:

Organism resistant to study drug
Concomitant antimicrobial therapy
Exclusion/Inclusion criteria violation - provided that the specific violation is noted
Never received study medication
Discontinuation due to adverse event(s)
Consent withdrawn (please provide reason)
Investigator withdrawal of patient (please provide reason)
Insufficient therapeutic response
Lost to follow-up (please provide reason)
Death
TOC outside the 5-11 day window (please provide reason)

Examples of exclusion categories, which should not be used include:

Protocol violation
No valid TOC urine culture

Also, please provide your interpretation regarding any by-treatment group imbalances in the rate of exclusion.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2387

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/s/

Jouhayna Saliba

7/17/03 11:13:22 AM

CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 28, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** 301-827-2387

Subject: Chemistry comments

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: May 28, 2003

TO: Andrew Verderame
Director, Regulatory Affairs

ADDRESS: Bayer Pharmaceutical Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172

FAX: 203-812-5029

FROM: Jouhayna Saliba

SUBJECT: NDA 21-554 (ciprofloxacin extended-release tablets, 1000 mg)

Please address the following CMC comments regarding your NDA:

1. Please submit general information for ciprofloxacin hydrochloride drug substance in the NDA (i.e. nomenclature, structure, and physicochemical properties). This should include information on [ ] and description of how [ ] in the drug substance.

2. Please submit general information for Ciprofloxacin [ ] drug substance in the NDA (i.e. nomenclature, structure, and physicochemical properties). This should include detailed information regarding [ ] of Ciprofloxacin [ ]

3. Please submit the specification for Ciprofloxacin [ ] that reflects revisions in the particle size distribution acceptance criteria and loss on drying previously agreed to for CIPRO XR, 500 mg (NDA 21-473).

4. Please provide in the NDA a specification (list of tests, acceptance criteria and analytical procedures) for ciprofloxacin hydrochloride drug substance.

5. Please include the test for water content as part of the specification for the drug product, CIPRO XR tablets, 1000 mg.

6. Please provide the following information with regards to the container/closure systems proposed for marketing of CIPRO XR tablets, 1000 mg:

   a) list of all materials and their respective DMFs that will be used in the commercial packaging components only;

   b) results of the physicochemical testing conducted on all the packaging components as per USP <661> (including light transmission) and moisture vapor permeation as per USP <671>;

   c) results of the — testing for unit-dose packaging components;

   d) confirmation that all packaging components comply with the appropriate sections of CFR.

7. Please provide updated (— months, if available) stability results for the primary stability batches and any available additional data for other supplemental batches included in the stability program.

8. Please provide the results of the statistical analysis studies performed on at least three NDA stability batches of the drug product, using the shelf-life-limiting attribute.

If you have any questions, please contact me at (301) 827-2387.

/S/

Jouhayna S. Saliba, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Product

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/s/

Jouhayna Saliba
5/28/03 02:19:27 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 22, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** 301-827-2387

Subject: Comments regarding report from study 100275 and the proposed PI dated 05/03

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: May 22, 2003

TO: Andrew Verderame
Director, Regulatory Affairs

ADDRESS: Bayer Pharmaceutical Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172

FAX: 203-812-5029

FROM: Jouhayna Saliba

APPLICATION: NDA 21-554

SUBJECT: Study 100275 and the proposed PI dated 5/03

- We note from the report of study BAY-Q3939-100275 that a significant treatment-by-infection-type interaction is present for the analysis of the primary efficacy endpoint (i.e., bacteriologic response at the test-of-cure visit). Internal analyses have indicated that while not statistically significant, trends towards the same type of interaction are also observed with the bacteriologic response at the follow-up visit. Please comment on the appropriateness of combining eradication rates for AUP and cUTI patients, in light of the observation that the treatment effect within each stratum may be different.

- It has come to our attention that the revised proposed package insert (dated 5/03) for uUTI and cUTI is missing information currently in the approved uUTI package insert which has not been indicated with a strikeout. Specifically, in the approved uUTI package insert, under CLINICAL STUDIES, Uncomplicated Urinary tract Infections (acute cystitis), there is a table containing eradication and clinical success rates in the clinical trial. The fourth line in the table is "Bacteriologic Eradication at TOC", the primary endpoint of the study. Eradication rates are shown for both Cipro XR and Cipro BID [i.e., 188/199 (94.5%) and 209/223 (93.7%), respectively]. In the proposed package insert (dated 5/03) these numbers have been omitted.

Please resubmit the proposed package insert with these numbers in the uUTI table reinserted. In addition, if you utilize a table for cUTI and AUP infections (study 100275), it should mirror the uUTI table.

If you have any questions, please contact me at (301) 827-2387.

/S/

Jouhayna S. Saliba, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Product

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/s/

Jouhayna Saliba
5/22/03 02:57:19 PM
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150 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: April 3, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** 301-827-2387

Subject: Comments on draft report submitted February 20, 2003

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: April 3, 2003

TO: Andrew Verderame
Director, Regulatory Affairs

ADDRESS: Bayer Pharmaceutical Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172

FAX: 203-812-5029

FROM: Jouhayna Saliba

APPLICATION: NDA 21-554

SUBJECT: Comments on the draft report submitted February 20, 2003

We refer to your submission dated February 20, 2003. We would like to thank you for providing the draft report for the Monte-Carlo simulations for various doses/durations/formulations of ciprofloxacin products in patients with varying degrees of renal insufficiency. Please address the following in your final report:

- Why was data from Study D84-024-2 (Ref. NDA 19-537) not used for simulations? This study has data for 250, 500 and 750 mg dose strengths in patients with various degrees of renal insufficiency.
- Please provide spaghetti plots for individual patient plasma concentration-time data generated using the simulations.
- Do you plan to submit additional internal/external validation results (prediction errors) as part of model validation?
- Please provide raw data of the IR formulations from the Renal Impairment studies (Study # 0622, 0953 and 0164) as part of the final report.
- Please refer to the Clinical Pharmacology Guidance on Population Pharmacokinetics (http://www.fda.gov/cder/guidance/index.htm) for details on submitting raw data used in the analysis.

NDA 21-554
CIPRO® XR
April 3, 2003

If you have any questions, please contact me at (301) 827-2387.

/S/

Jouhayna S. Saliba, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Product

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

/s/

Jouhayna Saliba
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 7, 2003

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** (301) 827-2387

Subject: request CRF

Total no. of pages including cover: 5

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-554
CIPRO® XR

Dear Mr. Verderame:

We refer to NDA 21-554, submitted October 29, 2002. Please provide the Case Report Forms for the following 10% random sample. Also, please include the microbiology data in these CRFs. If any of the CRFs for patients included in the sample have been previously submitted as part of the original NDA, please let us know where to find these patients.

You may choose to submit the above request either electronically or in paper. However, we would appreciate a paper copy.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2387

Patient Number (Protocol 100275)

100275-002-002028
100275-004-004002
100275-004-004005
100275-006-006012
100275-006-006016
100275-006-006022
100275-006-006024
100275-006-006029
100275-015-015021
100275-017-017005
100275-019-019001
100275-019-019011
100275-019-019014
100275-020-020001
100275-025-025005
100275-025-025011
100275-025-025015
100275-025-025018
100275-025-025027
100275-025-025028
100275-026-026026
100275-029-029041
100275-031-031012
100275-031-031035
100275-034-034001
100275-036-036009
100275-037-037006
100275-041-041027

NDA 21-554
CIPRO® XR

100275-042-042003
100275-042-042004
100275-042-042012
100275-042-042017
100275-042-042035
100275-042-042037
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100275-068-068001
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100275-073-073032

NDA 21-554
CIPRO® XR

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100275-082-082025
100275-086-086003
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100275-097-097001
100275-101-101007
100275-102-102001
100275-102-102014
100275-102-102019
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100275-120-120005
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100275-160-160003
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100275-209-209015
100275-209-209026
100275-211-211007

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/s/

Jouhayna Saliba

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

2. TELEPHONE NUMBER *(Include Area Code)*

(203) 812-5172

3. PRODUCT NAME
Cipro XR

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N #21-554

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

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

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4406

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, on reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

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

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

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

and

Food and drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Andrew L. Vanderslice	Director, Regulatory Affairs	10/29/02

FORM FDA 3397 (3/01)