DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-049
NDA 19-857/S-031
NDA 19-847/S-027
NDA 20-780/S-013

Bayer Pharmaceuticals Corporation
Attention: Mr. Andrew Verderame
Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Mr. Verderame:

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

Name of Drug Product	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
Cipro® (ciprofloxacin hydrochloride) Tablets, 100 mg, 250 mg, 500 mg and 750 mg	19-537	S-049	09-23-03	09-25-03
Cipro® IV (ciprofloxacin) 0.2% Solution in 5% Dextrose, 200 mg and 400 mg	19-857	S-031	09-24-03	09-29-03
Cipro® IV (ciprofloxacin) 1% Solution Vials, 200 mg, 400 mg and 1200 mg	19-847	S-027	09-24-03	09-29-03
Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%	20-780	S-013	09-24-03	09-29-03

We acknowledge receipt of your submissions dated:

January 26, 2004	March 12, 2004	March 19, 2004
January 30, 2004	March 17, 2004	March 24, 2004
February 12, 2004	March 18, 2004 (2)	March 25, 2004

These supplemental new drug applications provide for the use of Cipro® (ciprofloxacin) for the treatment of complicated urinary tract infections and pyelonephritis for pediatric patients (1 to 17 years of age) with the following information to be included in the **INDICATIONS AND USAGE** section of the final printed labeling.

> **Complicated Urinary Tract Infections and Pyelonephritis** due to *Escherichia coli*.
> NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert submitted on March 25, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-537/S0049, NDA 19-857/S-031, NDA 19-847/S-027, NDA 20-780/S-013." Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for these applications.

We remind you of your postmarketing commitments for the risk management program as discussed in a teleconference between Bayer and the Division on March 23, 2004. These commitments are listed below.

1. Bayer will voluntarily provide to the Division any promotional materials (4 weeks in advance) and press releases (1 week in advance) prior to distribution relating to the use of ciprofloxacin for complicated urinary tract infections and/or pyelonephritis in the pediatric population for three years following the approval of this supplemental application.
2. Bayer will provide biannual updates on CIPRO usage patterns in the pediatric population, with the submission dates being no later than October 31, 2004, April 30, 2005, October 31, 2005, April 30, 2006, October 31, 2006, and April 30, 2007 respectively.
3. Bayer will provide expedited (15 day) reporting to the Review Division and the Office of Drug Safety of all spontaneous adverse events (including listed events considered serious) in patients 17 years of age or younger until April 30, 2007.
4. Bayer will complete the 5 year observational study as per Protocol 100201 for patients receiving ciprofloxacin treatment. Bayer agrees to submit a final research report to the Division by March 2008.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected

summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for these products for the newly approved pediatric indications 4 weeks prior to distribution. We remind you of your agreement during our March 23, 2004 teleconference to include the complete text from the **INDICATIONS AND USAGE** section of the labeling in all promotional materials and advertisements for the pediatric complicated urinary traction infections and pyelonephritis indications, including the NOTE regarding efficacy, safety and preclinical information. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package inserts directly to:

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

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Yon Yu, Pharm D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Renata Albrecht

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