DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-052
NDA 19-847/S-030
NDA 19-857/S-035
NDA 20-780/S-016

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

Dear Mr. Verderame:

Please refer to your supplemental new drug applications dated March 5, 2004, received March 8, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number
Cipro® (ciprofloxacin hydrochloride) Tablets, 250 mg, 500 mg and 750 mg	19-537	S-052
Cipro® IV (ciprofloxacin) 1% Solution Vials, 200 mg, 400 mg and 1200 mg	19-847	S-030
Cipro® IV (ciprofloxacin) 0.2% Solution in 5% Dextrose, 200 mg and 400 mg	19-857	S-035
Cipro® (ciprofloxacin) Oral Suspension, 5% and 10%	20-780	S-016

We acknowledge receipt of your amendments to NDA 19-537/S-052 dated July 21, 2004 and NDA 19-847/S-030, 19-857/S-035 and NDA 20-780/S-016 dated January 7, 2005. We also acknowledge receipt of your amendment dated January 6, 2005 to all of the above-mentioned supplemental NDAs.

These supplemental new drug applications provide for the following changes to the **INDICATIONS AND USAGE**, **ADVERSE REACTIONS,** and **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION** sections of the package insert based on the information obtained from the Centers for Disease Control and Prevention program evaluation conducted after the bioterror events of October 2001:

Double underline = Added text

1. INDICATIONS AND USAGE SECTION

Under "**Inhalational Anthrax**" (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis:*

Ciprofloxacin serum concentrations achieved in humans served as a surrogate endpoint reasonably likely to predict clinical benefit and provided the initial basis for approval of this

indication[4]. Supportive clinical information for ciprofloxacin for anthrax post-exposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001. (See also **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION).**

2. ADVERSE REACTIONS SECTION

Under "**Post-Marketing Adverse Events**" after the final paragraph and before "**Adverse Laboratory Changes**", insert the following text:

Adverse events were also reported by persons who received ciprofloxacin for anthrax post-exposure prophylaxis following the anthrax bioterror attacks of October 2001 **(**See also **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION).**

3. INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION

Insert the following text as the 3rd and 4th paragraphs in this section:

More than 9300 persons were recommended to complete a minimum of 60 days of antibiotic prophylaxis against possible inhalational exposure to *B. anthracis* during 2001. Ciprofloxacin was recommended to most of those individuals for all or part of the prophylaxis regimen. Some persons were also given anthrax vaccine or were switched to alternative antibiotics. No one who received ciprofloxacin or other therapies as prophylactic treatment subsequently developed inhalational anthrax. The number of persons who received ciprofloxacin as all or part of their post-exposure prophylaxis regimen is unknown.

Among the persons surveyed by the Centers for Disease Control and Prevention, over 1000 reported receiving ciprofloxacin as sole post-exposure prophylaxis for inhalational anthrax. Gastrointestinal adverse events (nausea, vomiting, diarrhea, or stomach pain), neurological adverse events (problems sleeping, nightmares, headache, dizziness or lightheadedness) and musculoskeletal adverse events (muscle or tendon pain and joint swelling or pain) were more frequent than had been previously reported in controlled clinical trials. This higher incidence, in the absence of a control group, could be explained by a reporting bias, concurrent medical conditions, other concomitant medications, emotional stress or other confounding factors, and/or a longer treatment period with ciprofloxacin. Because of these factors and limitations in the data collection, it is difficult to evaluate whether the reported symptoms were drug-related.

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.

We approved supplemental new drug applications, NDA 19-537/S-038, NDA 19-847/S-024, NDA 19-857/S-027, NDA 19-858/S-021 and NDA 20-780/S-008, on August 30, 2000 under the regulations 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses.

Approval of these supplemental new drug applications, NDA 19-537/S-052, NDA 19-847/S-030, NDA 19-857/S-035 and NDA 20-780/S-016, fulfills your commitment in the August 30, 2000 approval

letter. We refer to your January 6, 2003 correspondence requesting withdrawal, under 21 CFR314.150, of approval of your NDA 19-858. Since you have requested withdrawal of approval of your NDA, you are released from the Subpart H commitment under 19-858/S-021.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (package insert submitted January 6, 2005).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs (January 1999) and Providing Regulatory Submissions in Electronic Format – Content of Labeling (February 2004)*. The guidances specify that labeling to be submitted in *pdf* format. To assist in our review of the FPL and future submission, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplements NDA 19-537/S-052, NDA 19-847/S-030, NDA 19-857/S-035 and NDA 20-780/S-016**." Approval of these submissions by FDA is not required before the labeling is used.

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.
Division Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Renata Albrecht

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