DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-069
NDA 19-847/S-043
NDA 19-857/S-050
NDA 20-780/S-027

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Janet Herrington, Ph.D.
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045

Dear Dr. Herrington:

Please refer to your supplemental new drug applications dated August 12, 2008, received August 13, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA	Supplement Number	Drug Product Name
19-537	S-069	CIPRO® (ciprofloxacin hydrochloride) Tablets, 250 mg, 500 mg, 750 mg
19-847	S-043	CIPRO® (ciprofloxacin hydrochloride) Intravenous 1% Solution Vials, 200 mg, 400 mg, and 1200 mg
19-857	S-050	CIRPO ® (ciprofloxacin hydrochloride) Intravenous 2% Solution in 5% Dextrose, 200 mg and 400 mg
20-780	S-027	CIPRO® (ciprofloxacin hydrochloride) Oral Suspension 5% and 10%

We acknowledge your submissions dated February 13, 2009.

These supplemental new drug applications provide for the addition of *Neisseria gonorrhoeae* and *Campylobacter jejuni* to the list of quality control (QC) organisms for *in vitro* susceptibility tests in the **MICROBIOLOGY/Susceptibility Tests/Dilution Techniques** subsection of the package insert.

We have 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. These supplemental new drug applications provide for the following changes to the content of labeling for the package insert (additions are noted with double underline and deletions noted with ~~strikethrough~~):

1. The **MICROBIOLOGY/Susceptibility Tests/Dilution Techniques** subsection of the package insert has been updated as follows:

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*, *Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, penicillin-susceptible *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*[a] :

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2–5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [b]:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the following MIC values:

Organism		**MIC (µg/mL)**
E. faecalis	ATCC 29212	0.25 – 2.0
E. coli	ATCC 25922	0.004 – 0.015
H. influenzae[a]	ATCC 49247	0.004 – 0.03
P. aeruginosa	ATCC 27853	0.25 – 1.0
S. aureus	ATCC 29213	0.12 – 0.5
C. jejuni[b]	ATCC 33560	0.06-0.25 and 0.03-0.12
N. gonorrhoeae[c]	ATCC 49226	0.001-0.008

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[b] *C. jejuni* ATCC 33560 tested by broth microdilution procedure using cation adjusted Mueller Hinton broth with 2.5-5% lysed horsed blood in a microaerophilic environment at 36-37°C for 48 hours and for 42°C at 24 hours[2], respectively.

[c] *N. gonorrhoeae* ATCC 49226 tested by agar dilution procedure using GC agar and 1% defined growth supplement in a 5% CO2 environment at 35-37°C for 20-24 hours[2].

2. The following publication was added to the **REFERENCES** section of the package insert.

   2. Clinical and Laboratory Standards Institute, Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline., CLSI Document M45-A**,** Vol. 26, No. 19, CLSI, Wayne, PA, 2006.

3. There have been minor editorial corrections of the footnotes throughout the package insert.

CONTENT OF LABELING

As soon as possible, but no later than one month from the date of this letter, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions "**SPL for approved supplements NDA 19-537/S-069, NDA 19-847/S-043, NDA 19-857/S-050 and NDA 20-780/S-027**."

In addition, within 21 days of the date of this letter, amend any pending applications for these NDAs with content of labeling in SPL format to include the changes approved in these applications.

Marketing the product with final printed labeling that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

We request that the revised labeling for the package inserts approved today be available on your website within 10 days of receipt of this letter and that the revised labeling be reflected in the next printing of the labeling. While you may use labeling already printed as of the date of this letter until May 13, 2009, after that date we request that the revised labeling accompany any newly shipped product.

Failure to make these changes promptly could make your product misbranded under Sections 201(n) and 502(a) of the FDCA.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MEDWATCH
Food and Drug Administration
Suite 12B05
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 Rebecca D. McKinnon, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Renata Albrecht

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