DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019537/S-083
NDA 019847/S-055
NDA 019857/S-063
NDA 020780/S-041

sNDA APPROVAL – ANIMAL EFFICACY

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Janet A. Herrington, PhD
Senior Director
100 Bayer Boulevard
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Herrington:

Please refer to your Supplemental New Drug Applications (sNDA), submitted under section 505(b) the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA #	Supplement #	Drug Product	Dosage	Letter Date	Receipt Date
019537	083	Cipro (ciprofloxacin hydrochloride) Tablets	250 mg, 500 mg	April 2, 2014	April 2, 2014
019847	055	Cipro IV (ciprofloxacin) for Intravenous Infusion		August 5, 2014	August 5, 2014
019857	063	Cipro IV (ciprofloxacin) for Intravenous Infusion – Flexible Container		April 2, 2014	April 2, 2014
020780	041	Cipro (ciprofloxacin) Oral Suspension		April 2, 2014	April 2, 2014

We acknowledge receipt of your amendments dated April 15, June 27, July 16, and January 23 and 29, 2014 (NDA 019537/S-083, NDA 019857/S-063 and NDA 020780/S-041). We also acknowledge receipt of your amendments dated December 19, 2014 and January 23 and 29, 2015, (NDA 019847/S-055).

These "Prior Approval" supplemental new drug applications propose to add to the label the indication for treatment and prophylaxis of plague due to *Yersinia pestis* in adults and pediatric patients from birth to 17 years of age.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, under the provisions of 21 CFR 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible), effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced animal efficacy regulations.

We note that your January 29, 2015, submission includes final printed labeling (FPL) for your package inserts and Medication Guide. We have not reviewed these FPLs. You are responsible for assuring that the wording in the printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and

annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART I APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

1. *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that ciprofloxacin can be safely used without restrictions on distribution or use.

2. *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that the FDA-Approved Medication Guide for Ciprofloxacin meets the requirements of this subsection. We remind you that the Medication Guide must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.

3. *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. We refer to your letter dated January 23, 2015, stating that you agree to conduct a field study to evaluate the efficacy and safety of Ciprofloxacin in the event of an attack with intentional release of *Y. pestis* in the United States and to submit a protocol for the field study on or before February 2016.

POSTMARKETING REQUIREMENT—SUBPART I

We remind you of your postmarketing requirement specified in your submission dated January 23, 2015. This requirement, along with any agreed upon completion dates, is listed below.

2843-1 Conduct a field study to evaluate the efficacy and safety of ciprofloxacin in the event of an attack with the intentional release of *Y. pestis* in the United States.

Final Protocol Submission:	02/2016
Study Completion:	To be determined should an event occur
Final Report Submission:	To be determined should an event occur

Submit the clinical protocol to your IND (b) (4) and IND (b) (4) for this product. Submit final reports to this NDA as a supplemental application. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this requirement 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/trials, number of patients entered into each study/trial. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart I Postmarketing Requirements**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in pediatric patients from birth to less than 17 years for this indication. Therefore, no additional studies are needed in pediatric patients.

PROMOTIONAL MATERIALS

Under 21 CFR 314.640, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.640, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

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 Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling

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

/s/

KATHERINE A LAESSIG
02/02/2015