DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203085

NDA APPROVAL

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Johnson:

Please refer to your New Drug Application (NDA) dated April 27, 2012, received April 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Stivarga (regorafenib) tablets, 40 mg.

We acknowledge receipt of your amendments dated April 30, 2012; May 3, 2012; May 16, 2012; May 24, 2012; June 4, 2012; June 7, 2012; July 3, 2012; July 13, 2012; July 24, 2012; July 30, 2012; August 13, 2012; August 24, 2012; August 28, 2012; September 10, 2012; September 21, 2012; September 26, 2012; and your September 27, 2012, email communication.

This new drug application provides for the use of Stivarga (regorafenib) tablets, for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 text for the patient package insert). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as submitted on September 21, 2012, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203085**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for regorafenib was not referred to an FDA advisory committee because this application did not raise significant safety or efficacy issues that were unexpected for a drug of this class in the intended population.

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease/condition does not exist in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of the serious risks of potentially prolonging the QT/QTc interval; potential drug interactions with substrates of

CYP2C8, CYP2C9 and CYP3A4; and potential impaired renal function related to the use of regorafenib.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of the serious risks of potentially prolonging the QT/QTc interval; potential drug interactions with substrates of CYP2C8, CYP2C9 and CYP3A4; and potential impaired renal function.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1925-1 **QT/QTc Interval Prolongation Assessment**

Complete a clinical trial evaluating the potential for regorafenib to prolong the QT/QTc interval in an adequate number of patients administered repeated doses of 160 mg of regorafenib and submit the final report, along with a thorough review of cardiac safety data.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	October 2012
Final Report Submission:	November 2012

1925-2 **Drug Interaction Assessment**

Complete a clinical trial and submit the final report to evaluate the effect of repeated doses of 160 mg of regorafenib on the pharmacokinetics of a probe substrate of CYP2C8, CYP2C9, CYP3A4 and CYP2C19.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	October 2012
Final Report Submission:	November 2012

1925-3 **Impaired Renal Function Assessment**

Conduct a multiple dose trial to determine the appropriate regorafenib dose in patients with severe renal impairment. Submit the final protocol for FDA review before conducting the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2013
Trial Completion:	December 2014
Final Report Submission:	June 2015

Submit the protocol(s) to your IND 75642, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1925-4 **Population Pharmacokinetic Analyses Assessment**

Submit an integrative population pharmacokinetic analysis report to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of regorafenib and its active metabolites M2 and M5.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2013

1925-5 **Exposure-Response Analyses Assessment:**

Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 using data collected from the CORRECT trial (Study 14387) in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapy.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Report Submission: November 2012

Submit clinical protocols to your IND 75642 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA

2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Monica Hughes, M.S., Lead Regulatory Project Manager, at (301) 796-9225.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
09/27/2012