

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204369Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

December 11, 2012

NDA: 204369

Drug Product Name

Proprietary: Stivarga Tablets, 40mg/tablet

Non-proprietary: Regorafenib (BAY 73-4505)

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
August 29, 2012	August 30, 2012	August 30, 2012	September 7, 2012
September 28, 2012	September 28, 2012	October 2, 2012	October 2, 2012
October 31, 2012	October 31, 2012	October 31, 2012	October 31, 2012
December 11, 2012	December 11, 2012 Email amendment	December 11, 2012	December 11, 2012

Submission History (for amendments only) – N/A

Applicant/Sponsor

Name: Bayer Health Care Pharmaceuticals

Address: P.O. Box 1000, Montville, NJ 07045

Representative: Phillip Johnson, Deputy Director, Global Regulatory Affairs.

Telephone: (973)-487-2868.

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
 2. **SUBMISSION PROVIDES FOR:** Original new drug application for Regorafenib tablets, 40 mg/tablet.
 3. **MANUFACTURING SITE:** Bayer Pharma AG, Leverkusen, Germany
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 40mg/tablet in a 45 mL bottle.
 5. **METHOD(S) OF STERILIZATION:** Oral Drug Product
 6. **PHARMACOLOGICAL CATEGORY:** Treatment of patients with
(b) (4)
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** The subject NDA 204369 is designated as a priority review submission for Regorafenib tablets. This is an electronic submission. During the filing review a deficiency was identified in the Validation of Analytical Procedures Section 3.2.P.5.3. The Microbial Limits Verification Test could not be located in this section or the submission. The sponsor was notified of this deficiency via an email dated September 19, 2012. The sponsor responded in a letter dated September 28, 2012 and this response is also reviewed here. On October 19, 2012 a second IR was sent to the sponsor with regard to their request for (b) (4) test. The sponsor responded to this IR on October 31, 2012 (3.2.P.-P.5.6.02.) and is also reviewed here. A third IR was sent via an email to Darshan Wariabharaj, Global Regulatory Strategist on November 29, 2012 informing Bayer that skip lot testing was not in compliance with 21 CFR211.165 (a) & (b) and the current NDMS/OPS policy. Bayer responded in an email on December 11, 2012 and the response is also reviewed here.

filename: N204369R1

Executive Summary**I. Recommendations**

- A. Recommendation on Approvability** – Recommend approval.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This drug product is an oral dosage form in 40 mg/tablet. The manufacturing process has the

(b) (4)

- B. Brief Description of Microbiology Deficiencies** – None
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D.
- B. Endorsement Block** _____
John W. Metcalfe, Ph.D.
- C. CC Block**
N/A

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/s/

VINAYAK B PAWAR
12/11/2012

JOHN W METCALFE
12/11/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204369

Applicant: Bayer Health Care

Letter Date: August 29, 2012

Drug Name: Regorafenib

NDA Type: Original NDA

Stamp Date: August 30, 2012

40 mg/tablets

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section P.3.3.01-04. The drug product is an oral tablet
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section P.3.5.01-01 The drug product is an oral tablet.
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?		X	No. This drug product is an oral tablet.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section P.5.6.01-01.
7	Has the applicant submitted the results of analytical method verification studies?		X	Process validation batch results were provided.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			N/A
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: none

Vinayak B. Pawar, Ph.D., OPS/NDMS/CDER

Date

John W. Metcalfe, Ph.D., OPS/NDMS/CDER

Date

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/s/

VINAYAK B PAWAR
09/18/2012

JOHN W METCALFE
09/18/2012
I concur.