CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204369Orig1s000

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEWER MEMORANDUM

To:	NDA 204,369
From:	Josephine Jee., CMC Reviewer, ONDQA
Thru:	Nallaperumal Chidambaram, Ph.D., Acting Chief, Branch II
Date:	31-JAN-2013
Drug:	Stivarga™(regorafenib)
Route of administration:	Tablet
Strength:	40 mg
Subject:	**Establishment Evaluation Recommendation**

Background

This review covers only the Establishment Evaluation for manufacturing facilities submitted by Bayer HealthCare Pharmaceuticals Inc. dated 18-MAY-2012. For further information on NDA 204369, please refer to NDA 203085 Stivarga™(regorafenib) CMC Review and NDA 204369 Stivarga™(regorafenib) Memoranda dated 11-DEC-2012, 22-JAN-2013 (Update), and 24-JAN-2013.

The recommendation for NDA 204369 is approval with respect to the chemistry, manufacturing, and controls (CMC) and acceptable recommendation from the Office of Compliance dated 29-JAN-2013; see attached FDA CDER EES, Establishment Evaluation Request Summary Report.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204369/000	**Sponsor:**	BAYER HLTHCARE
Org. Code:	107		340 CHANGEBRIDGE RD
Priority:			PINE BROOK, NJ 07058
Stamp Date:	30-AUG-2012	**Brand Name:**	Regorafenib
PDUFA Date:	28-FEB-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	30-DEC-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET; REGORAFENIB; 40MG

FDA Contacts:	J. MARTIN	Project Manager	(HFV-530)	3017962072
	J. JEE	Review Chemist		3017961375
	L. ZHOU	Team Leader		3017961781

Overall Recommendation:	ACCEPTABLE	on 29-JAN-2013	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 07-SEP-2012	by EES_PROD		

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9610135 **FEI:** 3002806462

BAYER PHARMA AG
CHEMPARK

LEVERKUSEN, , GERMANY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9610496 **FEI:** 3003229486		
	BAYER PHARMA AG 217-333 FRIEDRICH-EBERT STRASSE WUPPERTAL, , GERMANY		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

/s/

JOSEPHINE M JEE
01/31/2013

NALLAPERUM CHIDAMBARAM
01/31/2013
I concur.

CHEMISTRY REVIEWER MEMORANDUM

To:	NDA 204,369
From:	Josephine Jee., CMC Reviewer, ONDQA
Thru:	Nallaperumal Chidambaram, Ph.D., Acting Chief, Branch II
Date:	24-JAN-2013
Drug:	Stivarga™(regorafenib)
Route of administration:	Tablet
Strength:	40 mg
Subject:	**Environmental Assessment**

Background

This review covers only the Environmental Assessment Categorical Exclusion Request submitted by Bayer HealthCare Pharmaceuticals Inc. dated 18-MAY-2012. For further information on NDA 204369, please refer to NDA 203085 Stivarga™(regorafenib) and NDA 204369 Stivarga™(regorafenib) Memorandum dated 11-DEC-2012 and 22-JAN-2013 (Update).

Bayer HealthCare Pharmaceuticals, Inc. requests a categorical exclusion from the environmental assessment requirement for NDA 204369 under 21 CFR 25.31(b).

The Expected Introduction Concentration (EIC) of the active moiety in the aquatic environment is calculated to be (b) (4) ppb in the fifth year subsequent to the launch. This is below the threshold of 1.0 ppb at which the environment assessment must be conducted.

From this quantity, the Expected Introduction Concentration for regorafenib has been calculated according to FDA "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications", July 1998.

- EIC-Aquatic (ppb) = A × B × C × D
  where:

  A = kg/year produced as active moiety
  B = 1/Liters per day entering publicly owned treatment works (POTWs) estimated as 1.214×10^{11} L/day.
  C = 1/365 days
  D = 10^9 µg/kg (conversion factor)

  EIC-Aquatic average (ppb) = (b) (4) Kg × $(1/1.218 \times 10^{11}) \times (1/365) \times 10^9$
  = (b) (4) ppb

As EIC-Aquatic ((b) (4) ppb) represents a level below 1 ppb, Bayer HealthCare Pharmaceuticals, Inc., qualifies for the categorical exclusion under 21 CFR Part 25.31(b). There are no extraordinary circumstances that would prohibit the claim for a categorical exclusion for this NDA.

No further action is necessary for environmental assessment.

Furthermore, updated CMC information for Stivarga™(regorafenib) submitted in NDA 203085 is referenced in NDA 204369 Cover Letter dated 06-SEP-2012.

In conclusion, approval is recommended for NDA 204369 Stivarga™(regorafenib) pending satisfactory recommendation from the Office of Compliance.

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

/s/

JOSEPHINE M JEE
01/24/2013

NALLAPERUM CHIDAMBARAM
01/24/2013
This application is recommended for approval from the standpoint of Chemistry, manufacturing and controls pending overall acceptable recommendation from the Office of Compliance.

I concur.

CHEMISTRY REVIEWER MEMORANDUM

To:	NDA 204,369
From:	Josephine Jee., CMC Reviewer, ONDQA
Thru:	Nallaperumal Chidambaram, Ph.D., Acting Chief, Branch II
Date:	11-DEC-2012, 22-JAN-2013 (Update)
Drug:	Stivarga™(regorafenib)
Route of administration:	Tablet
Strength:	40 mg
Subject:	REVIEW (refer to NDA 203085 Chemistry Review dated 27-AUG-2012 and NDA 203085 Chemistry Reviewer Memorandum dated 12-SEP-2012)

Background

NDA 204369 is a 505 (b)(1) submission, the Quality Section was submitted on 31-MAY-2012 and the complete rolling submission was on 30-AUG-2012. This application was filed under priority review category. This application was assigned to this Reviewer on 18-JUN-2012. Bayer requested to cross-reference information from NDA 203085, Stivarga™(regorafenib), which was approved on 27-SEP-2012.

The recommendation for NDA 204369 is approval with respect to the chemistry, manufacturing, and controls (CMC) pending satisfactory recommendation from the Office of Compliance.

The proposed indication is for the treatment of patients with (b) (4)

Stivarga™ (regorafenib) Tablet, 40 mg, is a light pink, oval shaped film-coated tablet debossed with "BAYER" on one side, and "40" on the other side. Each tablet contains 40 mg of regorafenib which corresponds to 41.49 mg of regorafenib monohydrate and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film-coating contains the following inactive ingredients: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide. Regorafenib tablets are available in packages containing 84 tablets (NDC 50419-407-03). Each package contains three bottles. Each bottle contains 28 tablets.

Stivarga™ (regorafenib) Tablet, 40 mg, is stored at 25 °C (77 °F); excursions permitted to 15°–30° C (59° -86° F) in the original package. Bayer recommends "Do not remove the dessicant. Keep bottle tightly closed after first opening." Once the bottle is opened the medicinal product is to be discarded after (b) (4) days. (b) (4) These batches have also been used in phase III clinical studies. For clinical supply, the drug product is packed in (b) (4) bottles with (b) (4) dessicant capsule. The same pack was used for stability study. Another supportive stability study with another bulk batch of the

same manufacturing scale was started in 2010. The tablets in this batch were packed in smaller bottles (with same container closure system) which are used for commercial supply.

Regorafenib monohydrate is non-hygroscopic and the stable form at ambient conditions. The drug is practically insoluble in water and aqueous media with pH 1-13. The crystalline drug substance regorafenib monohydrate is (b) (4)

The only identified degradation product, which has actually been found in significant amounts above the reporting threshold of 0.1 % in the drug product, is (b) (4) The only other relevant degradation product is (b) (4) The formation of other potential degradation products is almost insignificant and below the identification threshold for drug products. Especially (b) (4) and (b) (4) have not actually been found in the drug product. They are regarded as only potential degradation products during production of the tablets which may theoretically be formed (b) (4) However, they are included in the test procedure for the unlikely case that any of the two (b) (4) occur in the drug product as (b) (4)

The following stability-indicating tests were performed at regular intervals: Appearance (color), dissolution, water content, (b) (4) any unspecified degradation product, sum of all degradation products, assay, and microbial purity. To date, 24 months real time data are available for 3 bulk batches packed in 90 mL and 120 mL bottles (primary stability). Additionally, 12 months data of another bulk batch in 45 mL HDPE bottles (b) (4) are available (supplemental stability). All batches are packaged in sealed

(b) (4) bottles, each containing a (b) (4) desiccant capsule. All stability results are within approved specification for Regorafenib Tablets. Regorafenib tablets are sensitive to thermal and humidity stress but they are stable upon exposure to light.

The carton and container labels are found acceptable by CMC and DMEPA on 11-SEP-2012.

The method validation testing from the Division of Pharmaceutical Analysis (DPA) in St. Louis recommended acceptable on 21-SEP-2012.

V. Pawar, Ph.D., Microbiology Reviewer recommended approval on 11-DEC-2012.

Previous NDA 203085 for Stivarga™ (regorafenib) Tablet, 40 mg for the treatment of patients with metastatic colorectal cancer (CRC) was approved on 27-SEP-2012. The current NDA 204369 is a Type 9 NDA, which by definition will be converted to an efficacy supplement under NDA 203085 upon approval of NDA 204369.

The CMC information and data submitted in the current NDA 204369 is the same as that submitted under NDA 203085. For reference, see Chemistry Review of NDA 203085 by Josephine Jee dated 27-AUG-2012, and Chemistry Reviewer Memorandum dated 12-SEP-2012.

Below is the Establishment Evaluation System (EES) Report as of 22-JAN-2013 remained the same as the attached report.

An overall OC recommendation: Pending

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204369/000	**Sponsor:**	BAYER HLTHCARE
Org. Code:	107		340 CHANGEBRIDGE RD
Priority:			PINE BROOK, NJ 07058
Stamp Date:	30-AUG-2012	**Brand Name:**	Regorafenib
PDUFA Date:	28-FEB-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	30-DEC-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET; REGORAFENIB; 40MG

FDA Contacts:	J. MARTIN	Project Manager	(HFV-530)	3017962072
	J. JEE	Review Chemist		3017961375
	L. ZHOU	Team Leader		3017961781

Overall Recommendation: PENDING on 07-SEP-2012 by EES_PROD

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9610135 **FEI:** 3002806462
BAYER SCHERING PHARMA AG
CHEMPARK
LEVERKUSEN, , GERMANY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: INSPECTION PERFORMED

Milestone Date: 05-OCT-2012

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9610496 **FEI:** 3003229486 BAYER SCHERING PHARMA AG 217-333 FRIEDRICH-EBERT STRASSE WUPPERTAL-ELBERFELD, , GERMANY		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	INSPECTION SCHEDULED		
Milestone Date:	02-NOV-2012		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

/s/

JOSEPHINE M JEE
01/24/2013

NALLAPERUM CHIDAMBARAM
01/24/2013

This application is recommended for approval from the standpoint of Chemistry, Manufacturing and Controls pending overall acceptable recommendation from the Office of Compliance.

I concur.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

NDA Number:	Supplement Number and Type:	Established/Proper Name:
204369	N/A	Regorafenib
Applicant:	**Letter Date:**	**Stamp Date:**
Bayer HealthCare Pharm.	31-MAY-2012	31-MAY-2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			EOP2 Meeting was held on 03-JUN-2009. Pre-NDA Meeting was held on 23-AUG-2011.

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NAI

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	Yes	
	III			Yes	
	III			Yes	
	III			Yes	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

File Name: N204369 Product Quality Filing Review

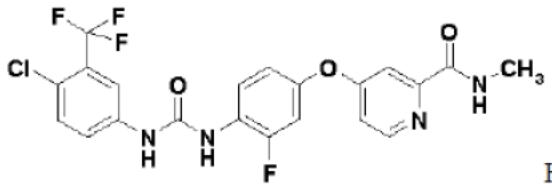
Version Date: 10-OCT-2012

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	X		No CMC fileability issues.
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	Describe potential review issues here or on additional sheets

Note: Regorafenib (INN) is a new chemical entity. Regorafenib is a novel oral multi kinase inhibitor administered for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

The chemical name for regorafenib is 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl] carbamoyl}amino)-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide.



H_2O

The drug substance regorafenib monohydrate is manufactured by Bayer Pharma AG, Wuppertal, Germany. The drug product described in this application is supplied as an immediate-release film-coated tablet containing 40 mg regorafenib for oral use. The tablets are manufactured by Bayer Pharma AG, Leverkusen, Germany.
Regorafenib monohydrate is the drug substance used for manufacture of regorafenib tablets. During the manufacturing process of regorafenib tablets (b) (4)

Regorafenib tablets for oral administration are available in a dose strength of 40 mg. The tablets contain the following inactive ingredients: cellulose microcrystalline, croscarmellose contains the following inactive ingredients: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA (ONDQA)

Josephine Jee} *11-OCT-2012*

Name of
~~Pharmaceutical Assessment Lead or CMC Lead~~ / CMC Reviewer Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

Nallaperumal Chidambaram

Name of
Branch Chief Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

File Name: N204369 Product Quality Filing Review

Version Date: 10-OCT-2012

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

/s/

JOSEPHINE M JEE
10/11/2012

NALLAPERUM CHIDAMBARAM
10/11/2012