

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203085Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Donghao Lu/Josephine M Jee, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: donghao.lu@fda.hhs.gov
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FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: 203085

Name of Product: STIVARGA® (Regorafenib) Tablets, 40 mg

Applicant: Bayer Healthcare Pharmaceuticals, Inc.

Applicant's Contact Person: Philip Johnson, Deputy Director, Global Regulatory Affairs

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

Telephone: (973) 487-2181 Fax: (973) 487-2016

Date Methods Validation Consult Request Form Received by DPA: 6/7/12

Date Methods Validation Package Received by DPA: 6/7/12

Date Samples Received by DPA: 7/5/12

Date Analytical Completed by DPA: 9/14/12

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: Analyst's comments are attached.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3897

Date: September 20, 2012

To: Donghao Lu, CDER, ONDQA, CMC Reviewer
Josephine M Jee, CDER, ONDQA, CMC Reviewer

Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis

From: Wei Ye, Chemist

Subject: Method Validation for NDA 203085
STIVARGA® (Regorafenib) Tablets, 40 mg
Bayer HealthCare Pharmaceuticals Inc.

The following methods were valuated and are acceptable for quality control and regulatory purposes:

1. (b) (4)
(Bayer Healthcare Pharmaceuticals Inc., Test Procedure S.4.2.01-02, Method A, Page 8 of 21)
2. Assay IDs & Impurities
(Bayer Healthcare Pharmaceuticals Inc., Test Procedure S.4.2.01-02, Method B, Page 13 of 21)
3. Assay & Impurities (HPLC1)
(Bayer Healthcare Pharmaceuticals Inc., Test Procedure P.5.2.01-03, Page 23 of 37)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to this method.

1. Assay & Impurities (HPLC1)
(Bayer Healthcare Pharmaceuticals Inc., Test Procedure P.5.2.01-03, Page 23 of 37)
 - On page 28, Section f) Linearity, a calculation formula needs to be given for clarification.
 - On page 32, Section Calculation for assay of regorafenib, the formula of dilution factor should be change to
$$f = \frac{100 \text{ mL} \cdot 50 \text{ mL}}{4 \text{ mL}} = 1250 \text{ mL}$$
 instead of (b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MICHAEL L TREHY
09/21/2012

BENJAMIN J WESTENBERGER
09/21/2012

ONDQA Division Director's Memo (updated)
NDA 203-085, STIVARGA (regorafenib) Tablets, 40 mg
Date: 14-SEP-2012

Reference is made to the 06-SEP-2012 Division Director's Memorandum for this application. All case details can be located in that memorandum. The previous memorandum states that all CMC review deficiencies have been resolved for this application, and all related reviews are complete. An overall acceptable recommendation from the Office of Compliance was issued for this application on 05-SEP-2012.

Reference is also made to the Chemistry Reviewer's 14-SEP-2012 update, which provides technical clarification regarding some of the resolved chemistry review issues. The 14-SEP-2012 memorandum also clarifies a discrepancy in the initial 30-AUG-2012 review, which confirmed an expiration dating period of (b) (4). The 14-SEP-2012 updates this confirmation by stating that the Applicant requested a 36 month shelf-life, which is granted based on their provided stability data. Additionally, the CMC reviewer's update states that the carton and container labels submitted on 11-SEP-2012 were found to be acceptable from a CMC standpoint.

There is no change to the previous ONDQA recommendation: all CMC review issues have been resolved, and ONDQA recommends approval of this NDA pending the submission of acceptable PI labeling. Due to the Agency's agreement with the Applicant's proposed expiration dating period of 36 months, no confirmatory language is needed in the approval letter when issued.

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/s/

SARAH P MIKSINSKI
09/14/2012

CHEMISTRY REVIEWER MEMORANDUM

To: NDA 203085
From: Josephine Jee., CMC Reviewer, ONDQA
Thru: Nallaperumal Chidambaram, Ph.D., Acting Chief, Branch II
Date: 12-SEP-2012
Drug: Stivarga™ (regorafenib)
Route of administration: Tablet
Strength: 40 mg
Subject: UPDATES

Note: I requested Liang Zhou to place my review in DARRTS on my behalf as I was going on leave during that time. I inadvertently forwarded an earlier version of my CMC-DP review for NDA 203085 to Liang Zhou, and the same was placed into DARRTS during my absence. The purpose of this Memorandum is to clarify some points that are missing in the uploaded version in DARRTS.

Background

NDA 203085 was submitted on 27-APR-2012 and filed under expedited priority review category. The CMC-DP review was completed on 27-AUG-2012 (GRMP date 30-AUG-2012). Since the applicant (b) (4)

(b) (4) in the manufacturing process of the drug product. During the Mid-Cycle of NDA 203085 (July 26, 2012), I conveyed my concerns to the Team and requested to send an IR to Bayer with the following comments:

1. Provide appropriate test(s) to confirm (b) (4)
2. Provide controls, including data, to limit the exposure to the conditions which cause (b) (4) critical to assuring the quality and efficacy of this product.
3. Provide a drug product (b) (4) Include appearance, identification, (b) (4) residual solvents, heavy metals, impurities, assay, residue on ignition, physical form, particle size distribution, and bulk density.
4. Provide analytical data to demonstrate that the (b) (4) is maintained throughout the shelf-life of Regorafenib Tablets. This test and the corresponding acceptance criterion should be included in the specification for Regorafenib Tablets.

The above comments were not forwarded to Bayer until 07-AUG-2012. Bayer responded to these comments on 13-AUG-2012. Bayer indicated that the assurance of the (b) (4) is determined by Dissolution testing as a surrogate for the content of the (b) (4) in the tablets. In addition, Bayer indicated that they were unable to perform (b) (4) because they (b) (4); therefore, they stated there will be too much interference. However, at the 15-AUG-2012

Teleconference with ONDQA, Bayer stated that they have performed (b) (4). I requested that they send their (b) (4) to us. Bayer submitted these (b) (4) on the 24-AUG-2012 Amendment.

The (b) (4) sent represented the (b) (4) for Regorafenib Tablets, Batch No. BX035FA after 6 months storage at 6°C and 40°C/75% RH; and 18 months at 25°C/60% RH; and after 24 months at 30°C/75% RH.

Comment: The analytical method for this (b) (4) was not validated as stated by Bayer and Bayer committed to validate this post-approval. The (b) (4) can only serve as a baseline for any changes in the Regorafenib Tablets for that particular batch.

I discussed the use of dissolution testing as a surrogate for the (b) (4) with the Biopharm reviewers, Dr. S. Suarez, and Dr. E. Chikhale, on 14-AUG-2012. They told me that there were previous approved NDAs using Dissolution testing as a surrogate for the content of the (b) (4) however, FDA recommends in this case tightening the acceptance criteria for the Dissolution testing. On 15-AUG-2012, FDA (R. Lostritto, S. Suarez, E. Chikhale, and J.Jee) discussed this issue with Bayer representatives. FDA recommended that in order to control the (b) (4) of Regorafenib Tablets, Bayer should tighten their Dissolution acceptance criteria to a more stringent one: $Q = (b) (4)$ at $t=30$ min. with stage testing according to USP, EP, and JP.

The testing for absence of (b) (4): dissolution after 45 min. with not less than (b) (4) (mean of 6 individual samples) without stage testing. If the mean dissolution rate of (b) (4) is not met, then (b) (4) testing is required to confirm that not more than (b) (4) of (b) (4) are present in the tablets (b) (4) testing methodology and specifications would not be implemented until it is submitted to FDA for approval).

Bayer sent an email dated 16-AUG-2012 (I made the wrong citation in my review indicating this communication came from FDA, see pages 15, 16, and 33 of my CMC-DP review in DARRTS) and the part of the communication content is as shown below:

In order to control the (b) (4) content of Regorafenib Tablets, Bayer and FDA agreed on the following:

Tightening of the dissolution specifications

- a) For QC testing: $Q = (b) (4)$, $t=30$ min with stage testing acc. to USP, EP, JP
- b) Testing for absence of (b) (4) dissolution after 45 min with not less than (b) (4) (mean of 6 individual samples) and without stage testing
- c) If mean dissolution rate of (b) (4) is not met, then (b) (4) testing is required confirming that not more than (b) (4) of (b) (4) are present in the tablets (b) (4) testing methodology & specifications would not be implemented until submitted to FDA post-approval)

Following the 16-AUG-2012 email, Bayer submitted an Amendment dated 24-AUG-2012 containing the information below.

- Updated specification (at release and at shelf-life) without (b) (4) as an attribute focusing on the revised dissolution testing as discussed in the 15-AUG-2012 Teleconference.
- Updated stability protocol.

- Dissolution Test Procedure.
- Update Stability data, including stability data for the (b)(4) container, Batch T145A01 at storage conditions: 25°C/60% RH (18 months); 30°C/75% RH (18 months), 40°C/75% RH (6 Months).

On 04-SEP-2012, I discussed with E. Chikhale, Biopharm Reviewer concerning the (b)(4) amount allowed as stated by Bayer and quoted in J.Jee's Review. Dr. Chikhale stated that this amount is unacceptable. However, I indicated to her that the representatives of FDA have not made any comments to Bayer in their communications concerning the (b)(4) in DP(15-AUG-2012 Teleconference and in Bayer's subsequent communications; 16-AUG-2012 email and 24-AUG-2012 Amendment).

At the end of this discussion, the Agency decided to send the following clarification via email to Bayer on 07-Sep-2012; see text below:

"Please note that the acceptance criterion for the (b)(4) was not agreed upon during the teleconference on 8/15/12, and that your suggested (b)(4) in the drug product will be a review issue when validated (b)(4) information (including justification for the proposed acceptance criterion) is submitted."

Bayer acknowledged on 07-SEP-2012: "We acknowledge FDA's comment that this proposed specification would be a review issue during the review of the (b)(4) method (to be submitted post-approval). Can you please confirm that there are no current review issues with regards to the updated dissolution specifications Bayer submitted in order to control the (b)(4) (b)(4) in the drug product?"

FDA confirmed to Bayer on 10-SEP-2012 that there are no current review issues with regards to the updated dissolution specifications Bayer submitted.

The uploaded version of my review in DARRTS did not clearly state the amount of shelf-life that was granted for Regorafenib Tablets. Dr. Liang Zhou recommended to grant (b)(4) of shelf-life based on 18 months of long-term stability data in (b)(4) bottles. Bayer had submitted 24 months of real time data (25°C/60% RH and 30°C/75 % RH) and 6 months at accelerated conditions (40°C/75% RH) for 3 primary stability batches packed in proposed package sizes: (b)(4); and 18 months of real time data (25°C/60% RH and 30°C/75 % RH) and 6 months at accelerated conditions (40°C/75% RH) for the (b)(4) bottles. **Bayer requested 36 months shelf-life, which was granted based on their stability data;** see ICH Q1E (When long-term data show little or no change and little variability, extrapolation of the shelf-life beyond the period covered by long-term data can be proposed. The proposed shelf-life can be up to twice as long as, but should not be more than 12 months beyond, the period covered by long-term data can be proposed).

The carton and container labels are found acceptable by CMC and DMEPA on 11-SEP-2012. DMEPA has pending labeling issues and will be communicated to Bayer soon.

We await method validation testing from the Division of Pharmaceutical Analysis (DPA) in St. Louis.

Also, the method validation for the (b) (4) and specification will be provided by Bayer at post-approval (Bayer committed to this; see Amendment dated 24-AUG-2012).

An overall acceptable recommendation for the manufacturing facilities dated 05-SEP-2012 was received from the Office of Compliance for NDA 203085 (see attached EES report).

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 203085/000	Sponsor:	BAYER HLTHCARE
Org. Code:	107		340 CHANGEBRIDGE RD
Priority:	1		PINE BROOK, NJ 07058
Stamp Date:	27-APR-2012	Brand Name:	Stivarga
PDUFA Date:	27-OCT-2012	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:		Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; REGORAFENIB; 40MG
FDA Contacts:	J. MARTIN	Project Manager	(HFV-530) 3017962072
	L. ZHOU	Team Leader	3017961781
<hr/>			
Overall Recommendation:	ACCEPTABLE	on 05-SEP-2012	by D. SMITH (HFD-323) 3017965321
	PENDING	on 01-MAY-2012	by EES_PROD
<hr/>			
Establishment:	CFN: (b) (4)	FEI: (b) (4)	(b) (4)
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE PACKAGER	OAI Status:	NONE
Profile:	TABLETS, PROMPT RELEASE		
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-MAY-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
<hr/>			
Establishment:	CFN: 9610135	FEI: 3002806462	
	BAYER SCHERING PHARMA AG CHEMPARK LEVERKUSEN, , GERMANY		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER	OAI Status:	NONE
Profile:	TABLETS, PROMPT RELEASE		
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-SEP-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**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: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-MAY-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: 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: 03-MAY-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

JOSEPHINE M JEE

09/14/2012

Memorandum to clarify the shelf-life of Regorafenib Tablets, EES updates, and Labeling updates.

NALLAPERUM CHIDAMBARAM

09/14/2012

I concur

ONDQA Division Director's Memo
NDA 203-085, STIVARGA (regorafenib) Tablets, 40 mg
Date: 06-SEP-2012

Introduction

STIVARGA (regorafenib) Tablets are formulated as light pink, oval-shaped film-coated tablets debossed with "BAYER" on one side and with "40" on the other. Each tablet contains 40 mg of regorafenib (b) (4) and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film-coating contains ferric oxides red and yellow, soy lecithin, polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

Regorafenib is indicated for the treatment of metastatic colorectal cancer who have been treated with, (b) (4) fluoropyrimidine-based chemotherapy. The recommended daily dose is 160 mg (4 tablets, 40 mg/tablet), to be taken once orally for three weeks followed by a one-week break.

All CMC review deficiencies have been resolved for this application, and all related reviews are complete. An overall acceptable recommendation from the Office of Compliance was issued for this application on 05-SEP-2012. All container/carton and PI labeling comments have been issued to the Applicant, and the receipt of final labeling is pending.

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA pending the receipt of final acceptable labeling (PI and container/carton). There is confirmatory language for the action letter, located at the end of this review, regarding the granted expiration dating period.

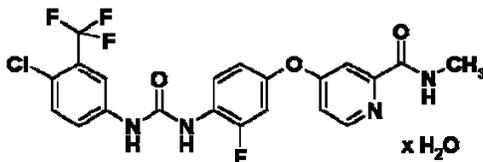
Administrative

The original submission of this 505(b)(1) NDA was received on 27-APR-2012. Several solicited CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (for the Drug Substance, 29-AUG-2012 by Dr. D. Lu), Chemistry Review #1 (for the Drug Product, 27-AUG-2012 by Ms. J. Jee) and the Biopharmaceutics Review (28-AUG-2012, Dr. E. Chikale).

The NDA is supported by IND 75,642 and four (4) drug master files (DMFs). All DMFs were assessed for adequacy in the respective chemistry reviews.

Drug Substance (regorafenib)

Chemical Name: 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl] carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate



Molecular Formula $C_{21}H_{15}ClF_4N_4O_3 \cdot (H_2O)$
Molecular Weight 500.83 g/mol

Regorafenib is a new molecular entity and is manufactured as its monohydrate. (b) (4)
Accordingly, regorafenib (water free) is the active drug substance present in regorafenib coated tablets. Regorafenib monohydrate is a (b) (4) is practically insoluble in aqueous solutions.

The Applicant employs a (b) (4) for the drug substance. This strategy was not altered during development. The Applicant identified and proposed Critical Process Parameters as part of the CMC dossier. The Application also provided adequate details in the Process Description. During the review, the Applicant was asked to provide a specification for an (b) (4), to provide additional justification for the proposed color specification, and to supply supporting information for methods validation. The Applicant's collective responses satisfactorily resolved these deficiencies during the CMC review.

The drug substance is relatively stable; no extraordinary storage precautions are required. The proposed re-test period of (b) (4) when stored in the recommended container closure system and under the proposed storage conditions (25°C/60%RH) is granted.

Drug Product – STIVARGA, 40 mg

STIVARGA (regorafenib) Tablets are formulated as light pink, oval-shaped film-coated tablets. Each tablet contains 40 mg of regorafenib (b) (4) and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film-coating contains ferric oxides red and yellow, soy lecithin, polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide. The drug product will be marketed in packages containing 84 tablets. Each package contains three bottles, and each bottle contains 28 tablets.

The manufacturing process consists of (b) (4). One of the most significant identified review issues centered around the Applicant's ability to sufficiently distinguish the presence of (b) (4) during manufacture. This issue was specifically discussed in a 15-AUG-2012 teleconference with the Applicant. While the technical issue was effectively resolved through this interaction, the Applicant stated an intent to submit further validation information for an (b) (4). The Agency confirmed that this submission could be made in the post-approval arena, via current regulations and guidance.

The Applicant also provided updated stability data on 24-AUG-2012, which was reviewed in this cycle. As captured in the Chemistry Review, these deficiencies/issues were resolved during the review clock. Related review information can be located in Chemistry Review #1 for the Drug Product, as well as the ONDQA Biopharmaceutics Review.

While all container/carton and PI labeling comments have been issued to the Applicant, acceptable final labeling has not yet been received.

The following language needs to be placed in the approval letter:

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/s/

SARAH P MIKSINSKI
09/06/2012

**STIVARGA[®] (Regorafenib)
Tablets
40 mg**

Bayer HealthCare Pharmaceuticals Inc.

Drug Substance Section

Division of Oncology Drug Products

**Donghao (Robert) Lu, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment**

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Chemistry Review Data Sheet

1. **NDA 203-085**
2. **REVIEW NUMBER:** 1
3. **REVIEW DATE:** 29 AUGUST 2012
4. **REVIEWER:** Donghao (Robert) Lu, Ph.D.
5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
--------------------	---------------

6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 203-085	27-APR-12
NDA 203-085 (Amendment 007)	3-JULY-12
NDA 203-085 (Amendment 0011)	13-AUG-12
NDA 203-085 (Amendment 0012)	24-AUG-12
NDA 203-085 (Amendment 0013)	28-AUG-12

7. **NAME & ADDRESS OF APPLICANT:**

NAME:	Bayer Healthcare Pharmaceuticals, Inc.
ADDRESS:	340 Changebridge Rd. Pine Brook, NJ 07058
REPRESENTATIVE:	Philip Johnson, Deputy Director, Global Regulatory Affairs
TELEPHONE:	973-487-2000

Chemistry Assessment Section

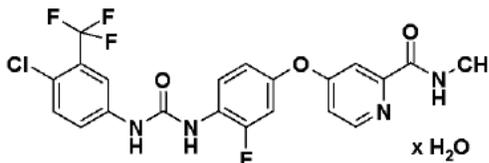
8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	STIVARGA (Regorafenib)
NON-PROPRIETARY NAME (USAN)	Regorafenib
CODE NAME/ NUMBER (ONDC ONLY)	BAY 73-4506
CHEMISTRY TYPE / SUBMISSION PRIORITY	1P

9. LEGAL BASIS FOR SUBMISSION: 505(b)1
10. PHARMACOL. CATEGORY: Multi kinase inhibitor
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 40 mg
13. ROUTE OF ADMINISTRATION: Oral
14. R_x/OTC DISPENSED: R_x OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (INN, USAN): Regorafenib
Name (CAS): 2-Pyridinecarboxamide, 4-[4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-fluorophenoxy]-N-methyl-, hydrate (1:1)
Name (IUPAC): 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate
(CAS) Registry Num: 1019206-88-2
Mol. Formula: C₂₁H₁₅ClF₄N₄O₃ · H₂O
Mol. Wt.: 500.83
Structural Formula:



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable (DS)	2-MAY-12	OC / CDER / FDA
OSE DMEPA	Acceptable (DP)	27-JUN-12	Jung Lee, RPh
EA	See DP		
Biopharm	See DP		
Pharm/Tox	Acceptable (DS)		Anwar M. Goheer, PhD
Micro Consultation	N/A		

The Chemistry Review for NDA 203-085

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The review includes the evaluation of the CMC information provided in the original NDA and amendments received through 8/28/2012. The regorafenib monohydrate drug substance is recommended as APPROVAL from a CMC perspective,

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is regorafenib monohydrate. The chemical name is 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl] carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate. It has a molecular formula of $C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$ and its molecular weight is 500.83.

Data from the studies of elemental analysis, UV, IR, Raman, NMR and MS demonstrated that the structure was adequately defined. The (b) (4) are adequate for the manufacturing of the regorafenib monohydrate drug substance. As this is a new molecular entity, a methods validation request was sent for the HPLC method for the determination of assay and organic impurities.

The impurities detected during the (b) (4) development of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities (b) (4) were adequately presented.

Regorafenib monohydrate drug substance was placed under the ICH recommended conditions for stability test. The drug substance was physically and chemically stable based on evaluation of the testing data. A retest period of (b) (4) was acceptable for the drug substance.

Chemistry Assessment Section

2. Drug Product

See drug product review document.

B. Description of How the Drug Product is Intended to be Used

See drug product review document.

C. Basis for Approvability or Not-Approval Recommendation

Bayer has submitted adequate CMC information to support the drug substance section in this NDA. All the remaining issues have been adequately addressed by the applicant (see the end of this document).

III. Administrative**A. Reviewer's Signature**

\s\ Donghao (Robert) Lu, Chemistry Reviewer

B. Endorsement Block

\s\ Nallaperum Chidambaram, Branch Chief (Acting)

C. CC Block

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/s/

DONGHAO R LU
08/30/2012

NALLAPERUM CHIDAMBARAM
08/30/2012
I concur.

NDA 203,085

Stivarga™ (regorafenib) Tablets (BAY 73-4506)

Bayer Healthcare Pharmaceuticals, Inc.

Josephine Jee

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

**For
Division of Drug Oncology Products 2
Office of Hematology and Oncology Products**

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Chemistry Review Data Sheet

1. NDA 203,085
Stivarga™(regorafenib)Tablets, (BAY 73-4506)
2. REVIEW #1
3. REVIEW DATE: 27-AUG-2012
4. REVIEWER: Josephine Jee ASSIGNED DATE: 03-MAY-2012
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 75,642	24-JUL-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original (CMC)	27-APR-2012
Serial No. 0001- Request for proprietary Name Review	30-APR-2012
Serial No. 0007 – CMC Information AMD	03-JUL-2012
Serial No. 0008 – Labeling Amendment	13-JUL-2012
Serial No. 0011 – Response to CMC IR dated 07-AUG-2012	13-AUG-2012
Serial No. 0012 – Response to CMC Telecon dated 15-AUG-2012	24-AUG-2012
Serial No. 13 – Response to CMC-DS IR	28-AUG-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer HealthCare Pharmaceuticals Inc.
Address: 340 Changebridge Rd
Pine Brook, New Jersey 07058
Representative: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
Telephone: (973) 487-2181

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Stivarga
- b) Non-Proprietary Name (USAN): Regorafenib
Code Name/# (ONDC only):
- c) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: P

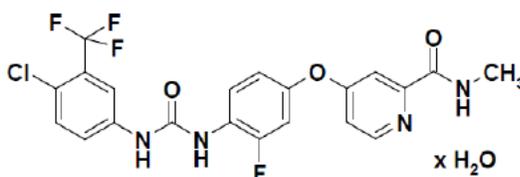
Executive Summary Section

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1), Regorafenib Tablets (BAY 73-4506),
10. PHARMACOL. CATEGORY: Treatment of metastatic colorectal cancer
11. DOSAGE FORM: Film-Coated Tablet
12. STRENGTH/POTENCY: 40 mg per Tablet
13. ROUTE OF ADMINISTRATION: Orally
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(b) (4)

Monohydrate: 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate

Chemical Structure of BAY-73-4506



Empirical Formula: $C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$

Molecular Weight: 500.83 (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	07-AUG-2012	J.Jee
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	17-FEB-2011	S.Dhanesar

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		(b) (4)				
(b) (4)	III		3	Adequate	14-FEB-2012	G. Holbert
	III		3	Adequate	31-JAN-2012	G. Holbert

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 75,642	Bayer HealthCare, Inc	Regorafenib Tablet	Active	20-JUL-2006	None

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
None			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections		M.Ramanadham	EES for this NDA is found to be acceptable on 05-September -2012
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)		A.Goheer/ Pending	Review is in progress.
Biopharm			E.Chikhale	Completed on 28-AUG-2012 – Approval is recommended.
ODS/DMEPA	Labeling consult		J.Schlick/ Pending	Carton and container labels and PI DMEPA recommends improvement to increase readability and prominence of important information to promote safe use of product.
Methods Validation			M. Trehy/ Pending	In progress.

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EA	N/A			Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	N/A		N/A	Not required for Solid Oral Dosage Form.

The Chemistry Review for NDA 203085

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application for Stivarga™ (regorafenib) Tablet, 40 mg is approval from the chemistry, manufacturing, and controls (CMC) perspective. The overall recommendation from the Office of Compliance for sites listed in EES is “acceptable”. The applicant and the Holders of the Type III Drug Master Files (DMFs) (b) (4) referenced in the NDA have provided adequate information. All CMC comments related to the carton and container label, and PI have been issued; see comments below. Based on Josephine’s review of stability data, a shelf life of (b) (4) can be granted. Store Stivarga at 25° C (77°F); excursions permitted to 15-30°C [59 - 86° F] USP Controlled Room Temperature.

The issues related to the identification of the (b) (4) in the drug product (b) (4) were resolved with Bayer; see Amendments dated 13-AUG-2012 and 24-AUG-2012. All pending labeling issues have been communicated to Bayer by DOP2, OHOP.

General Comments (communicated and pending):

1. Patients may have one carton containing three bottles dispensed to them. Once opened the tablets in a bottle expire after 28 days. To prevent patients from accidentally opening multiple bottles and possibly taking expired drug or wasting medication due to the short expiration, DMEPA recommends including a tamper evident seal on the cap or bottle if there isn’t one included already. The seal will assist patients in identifying which bottles have not been opened and serve as a reminder before opening a new bottle.
2. We acknowledge that the established name is at least half as large as the proprietary name, however, in accordance with 21 CFR 201.10(g)(2), the presentation of the established name should also “. . . have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features”. Therefore, we request you revise the established name (including dosage form) accordingly in each location it is presented.
3. Ensure that the carton and container use command language consistent with the PI.

Carton Labels:

1. Include the following statements on the principal display panel “Store in the original container to protect from moisture. Any remaining tablets should be discarded 28 days after opening the bottle.”
2. Revise “ – oral” to read “ – “for oral administration” to make a complete statement.

Executive Summary Section

3. Remove the statement on the back of the carton "Once opened, the product must be used in 28 days."
4. Include the statement "Attention Pharmacist: Dispense Stivarga in the original container" on the principal display panel.
5. Include the statement "Swallow tablets whole" on the principal display panel. Ensure the description is consistent with the package insert: "Stivarga tablets are supplied in packages containing three bottles, with each bottle containing 28 tablets, for a total of 84 tablets per package (NDC 50419-407-03). The light pink oval shaped tablets are debossed with "BAYER" on one side and "40" on the other side. Store Stivarga at 25° C (77°F); excursions permitted to 15-30°C [59 - 86° F] USP Controlled Room Temperature.
6. Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening. Discard any unused tablets 28 days after opening the bottle. Dispose of unused tablets in accordance with local requirements."

Container Label:

1. Include the statements "Once a bottle is opened, product must be used within 28 days. Bottle Opened: _____" on the principal display panel. Consider deleting the statement "-oral" to make room for this statement.
2. If the statement "-oral" is retained, revise it to read "- for oral administration" to make a complete statement.
3. Delete the Description statement on the side of the label as it is redundant.
4. Revise the statement on the side of the label "Store in original container" to read "Store in original container to protect from moisture."
5. We recommend deleting the circular Bayer logo. We are concerned this may cause confusion with the proposed description of regorafenib tablet.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessment**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Product**

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

Executive Summary Section

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 desiccant. Keep bottle tightly closed after first opening.” Once the bottle is opened the medicinal product is to be discarded after (b) (4). A 36 month expiry period in all climatic zones is proposed based on 24 months of long term and 6 months accelerated stability data from three (primary) Regorafenib Tablet batches which were manufactured by (b) (4). These batches have also been used in clinical phase III studies. For clinical supply the drug product is packed in HDPE bottles with (b) (4) desiccant 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 (b) (4). The drug is practically insoluble in water and aqueous media with pH (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).

Hence, both components are already properly controlled on the drug substance level. The formation of other potential degradation products is almost insignificant and below the identification threshold for drug products. Especially (b) (4) have not actually been found in the drug product. They are regarded as only potential degradation products during production of the tablets (b) (4). However, they are included in the test procedure (b) (4).

On 12-JUN-2012, this reviewer consulted with A. Goheer, Ph.D., Pharmacology/Toxicology Reviewer, concerning the acceptability of the acceptance criteria of the impurities in the drug product specification. He

Executive Summary Section

responded that there are no issues found in the qualification of the impurities in regorafenib drug substance or drug product. In addition, the levels of the impurities in the drug product are below the acceptance criteria of impurities in the drug substance and there are no new impurities/degradants found in the drug product. Since the levels of the impurities are qualified and found to be acceptable in the drug substance; therefore, the acceptability of the acceptance criteria in the drug product are also acceptable.

(b) (4)
On 07-AUG-2012, this reviewer sent the following comments to Bayer:

1. Provide appropriate test(s) to confirm the (b) (4).
2. Provide controls, including data, to limit the exposure to the conditions which cause (b) (4) critical to assuring the quality and efficacy of this product.
3. Provide a drug product (b) (4) Include appearance, identification, (b) (4), residual solvents, heavy metals, impurities, assay, residue on ignition, physical form, particle size distribution, and bulk density.
4. Provide analytical data to demonstrate that the (b) (4) is maintained throughout the shelf-life of Regorafenib Tablets. This test and the corresponding acceptance criterion should be included in the specification for Regorafenib Tablets.

On 13-AUG-2012, Bayer responded that the existence of the (b) (4) is confirmed by the dissolution testing. According to Dr. S. Suarez, CMC-Biopharm, she stated "Dissolution can be regarded as a surrogate for the content of the (b) (4) if tightening the dissolution acceptance criteria to a point that could use as an appropriate surrogate with adequate discrimination of batches with near zero (b) (4) content (e.g., % dissolved (b) (4) at 30 min). If the mean of six tablets is (b) (4) that result will trigger to perform (b) (4) on the finished tablet". This practice was communicated to Bayer on 15-AUG-2012 Teleconference. Dr. Suarez agreed that dissolution testing can be a surrogate for the content of the (b) (4) provided that the acceptance criteria of the dissolution testing are set more stringent (b) (4) at 30 min). Also the applicant will test dissolution at 45 min (release and stability). If the dissolution fails, Bayer has to provide confirmation by (b) (4). This was the topic of discussion during the 15-AUG-2012 Teleconference between FDA and Bayer. Before this Conference, Bayer did not submit (b) (4) data because the (b) (4) was not validated. Bayer stated that they will validate this method and will submit via an appropriate post-approval mechanism. From a scientific standpoint, the regular dissolution tests at release and during the stability study will adequately demonstrate that the (b) (4) is maintained throughout the shelf-life.

On the 24-AUG-2012 Amendment, Bayer provided copies of the (b) (4) revised drug product specifications at release and at shelf-life to include changes in the acceptance criteria for dissolution as agreed on the 15-AUG-2012 Telecon. However, (b) (4) was not included as a test in the drug product specification. It would be important to note that if dissolution failed in a batch, Bayer cannot rely on (b) (4) as an alternate test to prove the (b) (4) since it is not part of the drug specification.

Bayer provided long-term stability data for four pilot scale batches of regorafenib coated tablets 40 mg at 25°C/60% RH and 30°C/75% RH are provided covering a storage period of up to 24 months. Additionally, accelerated studies at 40°C/75% RH are reported for these batches covering 6 months of storage.

Executive Summary Section

The following stability-indicating tests were performed at regular intervals: Appearance (color), dissolution, (b) (4), (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 (b) (4) (primary stability). Additionally, 12 months data of another bulk batch in (b) (4) as foreseen for future commercial supply are available (supplemental stability). All batches are packaged in sealed HDPE bottles, each containing a (b) (4) desiccant capsule. All stability results are within the Regorafenib Tablet Specification. Regorafenib tablets are sensitive to thermal and humidity stress but they are stable upon exposure to light.

Drug Substance

Refer to D. Lu, Ph.D. Review for API.

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 160 mg regorafenib (4 tablets each containing 40 mg regorafenib), taken orally once daily for 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. The proposed indication is for the treatment of patients with metastatic colorectal cancer (CRC) who have been treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Approval for NDA 203-085 is based on the resolution of all CMC issues, including the manufacturing process and the quality control of the (b) (4) in the drug process by means of dissolution testing as a surrogate for the content of the (b) (4). An overall acceptable recommendation was received from the Office of Compliance on 05-SEP-2012. Method validation from the FDA Division of Pharmaceutical Analysis, St. Louis, MO will be conducted post-approval, and the method validation from Bayer for the (b) (4) will be provided via an appropriate post-approval submission. All labeling comments have been conveyed to the Applicant; however, the Applicant's final revision of the carton, container, and PI labeling is still pending.

III. Administrative

This NDA was submitted in electronic as a 505(b)(1) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block**C. CC Block**

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/s/

LIANG ZHOU
08/30/2012
for Chemist, Josephine Jee who is on leave

NALLAPERUM CHIDAMBARAM
08/30/2012
I concur.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	203-085
Submission Date	4/27/12
Product name, generic name of the active	Regorafenib
Dosage form and strength	Film Coated Tablet - 40 mg/tablet
Route of Administration	Oral
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
Clinical Division	Division of Oncology Products
Type of Submission	Original NDA – 505(b)(1)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		3.2.P.5.2.02-01 Proposed; Method: Apparatus 2, 900 mL of acetate buffer pH 4.5 with 0.1% SDS at 37 °C, at 75 rpm Acceptance Criteria: Q= (b) (4) at 30 min
3.	Does the application contain the dissolution method development report?	x		3.2.P.5.3.21 The report appears to have all required information.
4.	Is there a validation package for the analytical method and dissolution methodology?	x		3.2.P.5.3
5.	Does the application include a biowaiver request?		x	Not needed.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		Applicant states that regorafenib is a BCS Class II compound
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in vivo BA or BE information in the submission?	x		

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
10.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
13.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

5/29/12
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

5/29/12
Date

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

/s/

ELSBETH G CHIKHALE
05/29/2012

ANGELICA DORANTES
05/29/2012

PRODUCT QUALITY (Small Molecule) FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)

NDA Number:
203-085

Supplement Number and Type:

Established/Proper Name:
Regorafenib

Applicant: Bayer
Healthcare
Pharmaceuticals.

Letter Date: 27 April, 2012
(Resubmission)

Stamp Date:
27 April, 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?	Yes		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			EOP2 meeting was held on 3-June -2009. Pre-NDA meeting was held on 23-August, 2011

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		
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.			N/A

PRODUCT QUALITY (Small Molecule) FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	Yes		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	Yes		
9.	<p>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:</p> <ul style="list-style-type: none"> • 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) 	Yes		

PRODUCT QUALITY (Small Molecule) FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Yes		
-----	---	-----	--	--

* 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?	Yes		

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

PRODUCT QUALITY (Small Molecule) FILING REVIEW and IQA FOR NDA or Supplement (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?	Yes		
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?	Yes		
21.	Is there a batch production record and a proposed master batch record?	Yes		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Yes		
23.	Have any biowaivers been requested?			Fileable from ONDQA Biopharm. See Biopharm filing review in DARRTS.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Yes		
25.	Does the section contain controls of the final drug product?	Yes		
26.	Has stability data and analysis been provided to support the requested expiration date?			Review issue and Stat consult is needed
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		No	See additional note
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

PRODUCT QUALITY (Small Molecule) FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	Yes		Tablet (b) (4) is proposed

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?	Yes		LoA provided

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

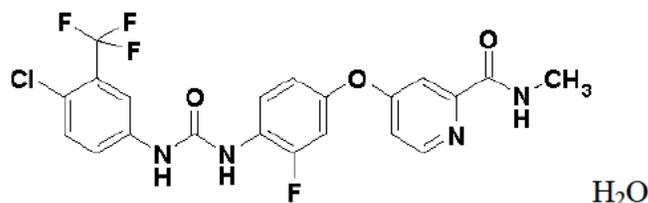
I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	Yes		
33.	Have the immediate container and carton labels been provided?	Yes		

PRODUCT QUALITY (Small Molecule) FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	Yes		
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.	Yes		No CMC fileability issue.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		No	

Note: Regorafenib ^{(b) (4)} 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, ^{(b) (4)} 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.



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.

^{(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

PRODUCT QUALITY (Small Molecule) FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)

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.

- Appropriate dissolution method needs to be reviewed by ONDQA Biopharm team
- Total impurities and individual impurity acceptance criteria should be evaluated. It appears that acceptance criteria might need to be tightened (also see Tox section).



(b) (4)

- Regorafenib monohydrate structure should be evaluated as the applicant claimed
- All sites for DS, DP and testing are already submitted into EES
- The statistical consult may need to be sent for the stability of DS and DP sections (refer to ICHQ1D and ICHQ1E).
- ^{(b) (4)} for the microbial limit testing is proposed and this will be a review issues since DP might be moisture sensitive.
- The CMC team review is recommended since this is designated as a priority NDA,

Liang Zhou

5-11-2012

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

Date

{Sarah Pope Miksinski}

5-11-2012

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

Date

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

/s/

LIANG ZHOU
05/11/2012

HARIPADA SARKER
05/11/2012
Acting for Sarah Pope-Miksinski