

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203341Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 203341, Bosulif® (bosutinib) Tablets
Date: 27-JUL-2012

Introduction

BOSULIF (bosutinib) Tablets are immediate-release tablets supplied in two strengths (100 and 500 mg). BOSULIF is indicated for the treatment of patients with relapsed or refractory chronic, accelerated or blast phase chronic myeloid leukemia. The daily dose is 500 mg, which may be either escalated (up to 600 mg) or reduced based on patient response and/or toxicity. Dose adjustments will occur using the developed dosage strengths, and tablets will not be altered for dosing adjustments.

ONDQA recommends approval of this NDA. There are no outstanding CMC deficiencies for this NDA.

Administrative

The original submission of this 505(b)(1) NDA was received 17-NOV-2011 from Wyeth Pharmaceuticals, Inc. (Collegeville, PA). Several solicited CMC amendments were also reviewed during the review cycle. The Chemistry, Manufacturing and Controls assessment is captured in the following reviews, respectively: Chemistry Reviews #1 and #2 (by Dr. J. Crich, dated 18-JUL-2012 and 23-JUL-2012, respectively), and the ONDQA Biopharmaceutics Review #1 (by Dr. A. Khairuzzaman, dated 15-MAY-2012).

The NDA is supported by IND 68,268 and nine (9) drug master files (DMFs). Primary CMC reviews, including the ONDQA Biopharmaceutics review, confirm approval recommendations, and all primary reviews confirm that there are no outstanding CMC deficiencies.

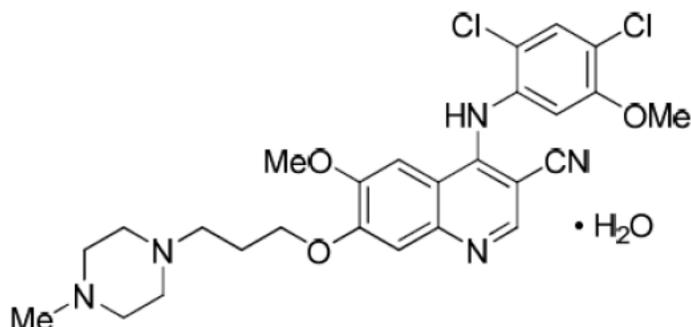
An overall acceptable recommendation from the Office of Compliance was received on 10-MAY-2012. Acceptable labeling, including container/carton labels, was negotiated and finalized during the review clock.

The following language needs to be placed into the action letter:

An expiration dating period of 24 months is granted for the drug product, when stored at 25°C (77°F) excursions permitted between 15°C to 30°C (59°F to 86°F).

Drug Substance (bosutinib)

Chemical Name: 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate (1:1)



Bosutinib is a new molecular entity. It is a white to yellowish tan powder. It is classified as a BCS Class 4 compound (low solubility, low permeability) with pH-dependent solubility. It is nonhygroscopic. The morphic form selected for development and commercialization (b) (4)

(b) (4)
Detailed information regarding the designation of the (b) (4) starting materials, the commercial sources, acceptance criteria, and associated methods of analysis are provided and were determined to be acceptable during the review.

A Quality by Design (QbD) approach was employed for the manufacturing process based on the principles outlined in ICH Q8, Q9 and Q11, including the development of a quality target product profile (QTPP), identification of the potential critical quality attributes (CQAs), and the designation of operating ranges for each step of the process. The Applicant used a statistically designed multivariate experimental (DoEs) approach to propose the overall operating ranges and control strategy for the manufacturing process. The quality attributes of bosutinib monohydrate are defined in the drug substance specification based on a traditional approach. The key and critical process parameters and ranges for each manufacturing step are provided, as well as the regulatory commitment for handling movements associated with the operating ranges for these. The Applicant's approach was deemed to be acceptable as changes to other parameters would be reported in accordance with 21 CFR 314.70 (see pages 15-19 of Chemistry Review #1).

The proposed re-test period of (b) (4) is granted for the drug substance, when packaged in the proposed container closure system and stored at controlled room temperature.

Drug Product (Tablets, 100 and 500 mg)

Bosulif® (bosutinib) Tablets are available in 100 mg and 500 mg dosage strengths. The tablets contain bosutinib monohydrate as the active pharmaceutical ingredient (equivalent to 100 mg and 500 mg of anhydrous bosutinib). Excipients include microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and an iron oxide coloring component (yellow for the 100 mg

tablet, and red for the 500 mg tablet). All excipients are conventional for solid oral dosage forms. (b) (4)

(b) (4)

Standard release specifications for a solid oral dosage form are proposed. The commercial packaging is 60-count HDPE bottles. The Applicant proposed a 24 month expiry for this product when stored in the commercial packaging at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Based on the stability data provided, the Agency grants a 24 month expiry for the drug product, as packaged in the commercial configuration and when stored at USP controlled room temperature.

The proposed commercial container closure system for both strengths consists of a 60-mL HDPE polyethylene bottle/closure with dessicant. The 100 mg tablets will be packaged in a 120-count configuration, while the 500 mg tablets will be packaged in a 30-count configuration. The Applicant employed a matrixed stability protocol design conducted on 100-count configurations of both dosage strengths. The original NDA included stability data from three primary batches for both dosage strengths, covering up to 24 months at 25°C/60% RH and 30°C/75% RH, and up to 6 months at 40°C/75% RH. As stated in Chemistry Review #1 (page 10), the provided data support the proposed 24 month expiration dating period for both strengths of the drug product as packaged in HDPE bottles and stored at controlled room temperature.

Chemistry Review #1 (pages 187-191) also notes that there are differences in the proposed container/closure system intended for marketing and that used in the primary stability studies. Therefore, the reviewer assessed the comparability of the primary stability configuration with that proposed for commercialization as part of the review. The Applicant provided calculations for moisture absorption capacity of desiccant canister and total available moisture within the commercial container closure system to justify the proposed shelf life in the proposed commercial container closure system. The configurations were determined to be sufficiently comparable, and the provided stability data package was determined to be acceptable in support of the proposed expiration dating period of 24 months.

Due to the lack of stability data for the proposed commercial configuration, the Agency requested revisions to the Applicant's post-approval stability protocol based on ICH Q1A(R2) (see pages 191-193 of Chemistry Review #1). Specifically, the Agency requested that the post approval stability commitment include a 6-month accelerated study along with the long-term studies to be conducted through the proposed shelf life for the first three production batches of bosutinib (both dosage strengths). The requested revisions had not been received by the Agency at the time of finalization for Chemistry Review #1, and therefore, the recommendation at that time was for a Complete Response pending resolution of the final post approval stability protocol. Chemistry Review #2 confirms that the Applicant's post approval stability protocol had been revised appropriately, and the deficiency was satisfactorily resolved.

During the review, the chemistry team discussed multiple options regarding the possible resolution of the post approval stability protocol, including the filing mechanism for updated stability data generated from the protocol itself (see pages 193-194 in Chemistry Review #1). The issue was ultimately discussed by the inclusive team in a 16-JUL-2012 internal meeting. Attendees included Dr. J. Crich, Dr. D. Ghosh, Ms. J. Brown, and Dr. S. Pope Miksinski. These discussions are captured in Chemistry Review #1. At the conclusion of this meeting, all attendees

agreed that the deficiency noted in the post approval stability protocol did not impart a significant risk to overall product quality. The identified review issue was satisfactorily resolved in Chemistry Review #2, in which the reviewer confirms the acceptability of the revised post approval stability protocol (pages 13-14).

Final labeling negotiations included discussion regarding the Applicant's proposed statement of "MADE IN SPAIN" on the container labels. The CMC team deferred a final determination on this issue to the Office of Compliance (Ms. Jean McCue), who confirmed that the statement should be retained for conformance with current US Customs requirements. Please refer to page 14 of Chemistry Review #2 for additional information.

Please place the following language in the action letter:

An expiration dating period of 24 months is granted for the drug product, when stored at 25°C (77°F) excursions permitted between 15°C to 30°C (59°F to 86°F).

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

/s/

SARAH P MIKSINSKI
07/27/2012

NDA 203341

Bosulif[®] (bosutinib) Tablets

Wyeth Pharmaceuticals, Inc.
(a Wholly Owned Subsidiary of Pfizer, Inc.)

CMC Review # 2

Joyce Crich, Ph.D

Review Chemist

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

**CMC REVIEW OF NDA 203341
For the Division of Hematology Products**

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CMC Review Data Sheet

1. NDA 203341
2. REVIEW #: 2
3. REVIEW DATE: 23-July-2012
4. REVIEWER: Joyce Crich, Ph.D
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 68,268 submission	19-Apr-2004
Original IND 68,268 CMC review	24-May-2004
CMC end-of-phase-2 meeting (10-Jul-2008) minutes	01-Aug-2008
CM Review #1 for NDA 203341	20-Jul-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	17-NOV-2011	17-NOV-2011
Amendment (Response to 26-Jan-2012 CMC IR regarding dissolution)	9	06-Mar-2012	06-Mar-2012
Updated Drug Product Analytical Methods and Validation of Analytical Procedures	12	19-Mar-2012	19-Mar-2012
Amendment (BC) (Response to FDA 23-Mar-2012 CMC IR)	13	05-APR-2012	05-APR-2012
Drug Product Manufacturer Information Update	17	03-May-2012	03-May-2012
Amendment (Response to 03-May-2012 CMC IR and 16-Apr-2012 IR regarding microbial purity)	18	16-MAY-2012	16-MAY-2012
Amendment (Response to 24-May2012 telecon)	20	31-MAY-2012	31-MAY-2012
Amendment (Updated post-approval stability protocols for DP --response to 18-Jul-2012 CMC request)	22	19-Jul-2012	19-Jul-2012

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Wyeth Pharmaceuticals, Inc.
(a Wholly Owned Subsidiary of Pfizer, Inc.)
Address: 500 Arcola Road, Collegeville, PA 19426-3982
Representative: Carl M. DeJuliis, PharmD,
Director, Worldwide Regulatory Strategy
Telephone: (860) 441 - 1693

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Bosulif[®]
b) Non-Proprietary Name: bosutinib tablets
c) Code Name/# (ONDQA only): bosutinib monohydrate (drug substance)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1 (new molecular entity)
 - Submission Priority: S (standard review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Dual Src Bcr-Abl tyrosine kinase inhibitor

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 100 mg and 500 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

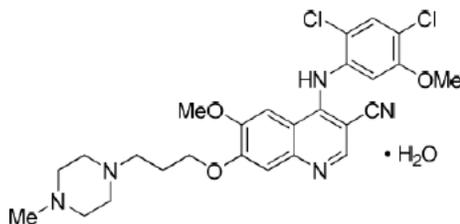
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

CMC Review Data Sheet

Chemical Structure	
Molecular Formula	C ₂₆ H ₂₉ Cl ₂ N ₅ O ₃ •H ₂ O
Molecular Weight	548.46 (monohydrate) 530.46 (anhydrous)
United States Adopted Name (USAN)	bosutinib monohydrate
Chemical Name	3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-, hydrate (1:1).
Chemical Abstracts Service (CAS) Registry Number	CAS-380843-75-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4	Adequate	28-Feb-2012	See sections 1.4.1 & 3.2.P.4.1
	IV		4	Adequate	28-Feb-2012	See sections 1.4.1 & 3.2.P.4.1	
	III		4	Adequate	28-Feb-2012	See sections 1.4.1 & 3.2.P.7	
	III		3 & 4	Adequate	17-Feb-2012	Reviewed by Dr. Xuhong Li	
	III		3 & 4	Adequate	17-Feb-2012	Reviewed by Dr. Xuhong Li	
	III		3 & 4	Adequate	16-Jun-2011	Reviewer by Dr. George Lunn	
	III		3 & 4	Adequate	11-Mar-2005 & 09-Sep-2003	Reviewed by Dr. Gene Holbert & Dr. Edwin Jao See sections 1.4.1 & 3.2.P.7	
	III		3 & 4	Adequate	23-Jun-2006	Reviewed by Josephine Jee See sections 3.2.P.2.4 & 3.2.P.7	

¹ Action codes for DMF Table:
1 – DMF Reviewed.

CMC Review Data Sheet

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
IND	68,268	Bosutinib (SKI-606)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10-May-2012	D. Smith
Pharm/Tox	Impurity limits in drug substance are acceptable	17-Jul-2012	Shwu Luan Lee
Biopharm	Acceptable	15-May-2012	Akm Khairuzzaman
LNC	N/A		
Methods Validation	Acceptable	04-May-2012	Daniel J Mans
DMEPA*	The proposed proprietary name, Bosulif is acceptable	03-Feb-2012	Kimberly De Fronzo
EA	Categorical exclusion accepted (see CMC Review #1)	20-Jul-2012	Joyce Crich
Microbiology	approval from microbiology product quality standpoint	12-Jun-2012	Robert Mello

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 203341

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Include the following language in the approval letter:

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product bosutinib tablets (100 mg and 500 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance bosutinib is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Detailed information regarding designation of the [REDACTED] (b) (4) starting materials, the commercial sources, acceptance criteria, and associated methods of analysis are provided.

A Quality by Design (QbD) approach was employed for the manufacturing process based on the principles of ICH Q8, Q9 and Q11, including quality target product profile (QTPP), identification of the potential critical quality attributes (CQAs), the process parameters (CPP, KPP) that have a potential impact on these CQAs, and operating spaces for each step of the drug substance manufacturing process by statistically designed multivariate experimental (DoEs) approaches, leading to the overall operating space and control strategy for the manufacturing process. The quality attributes of bosutinib monohydrate are defined in the drug substance

CMC Assessment Section

specification based on a traditional approach. The key and critical process parameters for each manufacturing step are provided, as well as the regulatory commitment for the operating range.

Bosutinib monohydrate is a white to yellowish tan powder. It is classified as a BCS Class 4 compound (low soluble and low permeable material) with pH dependent solubility. It is non-hygroscopic. The selected polymorph form (b) (4) of bosutinib monohydrate for development and commercialization is the (b) (4)

The submitted stability data support the proposed retest period of (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

(2) Drug Product

Bosulif[®] (bosutinib) tablets are available in 100 mg and 500 mg dosage strengths. The tablets contain bosutinib monohydrate as the active pharmaceutical ingredient equivalent to 100 mg and 500 mg of bosutinib anhydrous together with microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow (for 100 mg tablet) and iron oxide red (for 500 mg tablet).

Bosulif[®] (bosutinib) tablets are available for oral administration in two strengths: a 100 mg yellow, oval-shaped, biconvex, immediate release film coated tablet with debossed with "Pfizer" on one side and "100" on the other; Bosutinib film coated tablets, a 500 mg red, oval-shaped, biconvex immediate release film coated tablet with "Pfizer" on one side and "500" on the other. Bosulif[®] (bosutinib) tablets are supplied in 60 ml HDPE bottles of 120 tablets for 100 mg strength and of 30 tablets for 500 mg strength.

The applicant submitted the stability data from three primary batches for the 100 mg strength and 500 mg strength tablets up to 24 months at 25°C/60% RH and 30°C/75% RH, and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the drug

CMC Assessment Section

product in both strengths packaged in HDPE bottles and stored at controlled room temperature. Additionally, the submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

The NDA submission did not include any stability data for the proposed commercial container closure system which is different from the primary stability container closure system (e.g. configuration, fill volume, headspace, MVTR, and amount of desiccant). According to ONDQA's Initial Quality Assessment and Filling Review for this NDA dated 21-Dec-2011 in DARRTS, the issue of lacking stability data for the proposed commercial container closure system was determined as a review issue. During this review cycle, instead of providing any stability data for the proposed commercial container closure system after Agency's information request for such data, the applicant provided the calculations for moisture absorption capacity of desiccant canister and total available moisture within the commercial container closure system to justify the proposed shelf life in the proposed commercial container closure system. The provided justification appears to be reasonable, but it does not completely exclude possible impact on quality attributes linked to water content due to the potential difference in moisture level control. Although the risk of changing container closure system for solid dosage form is relatively low, the provided theoretical calculation of moisture exposure (MVTR vs. desiccant capacity) is only a supporting data for moisture-barrier equivalence, and is not a replacement for stability study result from the proposed container closure system. According to ICH Q1A(R2) Section II(B)(4), Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Therefore, it is recommended that the Postapproval Stability Commitment be revised to include accelerated studies for 6 months along with the long-term studies through the proposed shelf life for the first three production batches of bosutinib 100 mg and 500 mg tablets, to monitor the stability trend and to confirm the shelf life, based on ICH Q1A(R2) Section II(B)(8) (refer to the Letter of Information Request dated 18-Jul-2012). The applicant provided adequate response and revised the Postapproval Stability Commitment accordingly in the Amendment of 19-Jul-2012.

The recommendation and conclusion on the approvability for this NDA are made by incorporating QBD principle, risk management, and scientific rationale based on the stability data from the primary stability study container closure system, provided that the firm committed to conduct the postapproval stability studies and to monitor the stability of marketed drug products in the proposed commercial container closure system according to ICH Q1A(R2) II(B)(8) (refer to revised the Postapproval Stability Commitment in Section P.8.2). The CMC reviewer does not think this special situation with relative low risk to product quality (under the circumstance of lacking stability data for the proposed commercial container closure system at filing was determined as a review issue) should be viewed as a precedent in general for other future NDA submissions as any scenario of container closure system varies from each other and very much depends on the nature of drug product.

CMC Assessment Section

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

Bosulif[®] (bosutinib) Tablets are indicated for the treatment of chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance, or intolerance to prior therapy.

Bosulif[®] (bosutinib) Tablets are dosed orally with food. The recommended dose and schedule of Bosulif is 500 mg once daily. Dose adjustments may be required for hematologic and non-hematologic adverse reactions.

C. Basis for Approvability or Not-Approval Recommendation

The applicant provided adequate response to Agency's Letter of Information Request dated 18-Jul-2012 and revised the Postapproval stability commitment accordingly in the Amendment of 19-Jul-2012. The deficiency identified as the basis for a Not-Approval Recommendation in CMC Review #1 has been addressed satisfactorily.

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Bosulif.

Methods validation was completed on 04-May-2012 by the FDA St. Louis Laboratory for the drug substance and drug product analysis which are confirmed to be acceptable for quality control and regulatory purposes. Note: it is not required for approval of the NDA.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 10-Jul-2012 are acceptable from the CMC perspective.

The Office of Compliance issued an overall "acceptable" recommendation dated 10-May-2012 for all facilities used for manufacturing and control of the drug substance and drug product.

CMC Assessment Section

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

(See appended electronic signature page)

Joyce Crich, Ph.D, Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Debasis Ghosh, Ph.D., Acting CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Janice Brown, Acting Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

JOYCE Z CRICH
07/24/2012

JANICE T BROWN
07/24/2012

NDA 203341

Bosulif[®] (bosutinib) Tablets

Wyeth Pharmaceuticals, Inc.
(a Wholly Owned Subsidiary of Pfizer, Inc.)

Joyce Crich, Ph.D

Review Chemist

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

**CMC REVIEW OF NDA 203341
For the Division of Hematology Products**

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CMC Review Data Sheet

1. NDA 203341
2. REVIEW #: 1
3. REVIEW DATE: 18-July-2012
4. REVIEWER: Joyce Crich, Ph.D
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 68,268 submission	19-Apr-2004
Original IND 68,268 CMC review	24-May-2004
CMC end-of-phase-2 meeting (10-Jul-2008) minutes	01-Aug-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	17-NOV-2011	17-NOV-2011
Amendment (Response to 26-Jan-2012 CMC IR regarding dissolution)	9	06-Mar-2012	06-Mar-2012
Updated Drug Product Analytical Methods and Validation of Analytical Procedures	12	19-Mar-2012	19-Mar-2012
Amendment (BC) (Response to FDA 23-Mar-2012 CMC IR)	13	05-APR-2012	05-APR-2012
Drug Product Manufacturer Information Update	17	03-May-2012	03-May-2012
Amendment (Response to 03-May-2012 CMC IR and 16-Apr-2012 IR regarding microbial purity)	18	16-MAY-2012	16-MAY-2012
Amendment (Response to 24-May2012telecon)	20	31-MAY-2012	31-MAY-2012
Amendment (container and carton labeling)			
Amendment (Updated post-approval stability protocols for DP --response to 18-Jul-2012 CMC request)	pending	pending	pending
Amendment (Revised container and carton labeling)	pending	pending	pending

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Wyeth Pharmaceuticals, Inc.
(a Wholly Owned Subsidiary of Pfizer, Inc.)
Address: 500 Arcola Road, Collegeville, PA 19426-3982
Representative: Carl M. DeJuliis, PharmD,
Director, Worldwide Regulatory Strategy
Telephone: (860) 441 - 1693

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Bosulif[®]
b) Non-Proprietary Name: bosutinib tablets
c) Code Name/# (ONDQA only): bosutinib monohydrate (drug substance)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1 (new molecular entity)
 - Submission Priority: S (standard review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Dual Src Bcr-Abl tyrosine kinase inhibitor

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 100 mg and 500 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

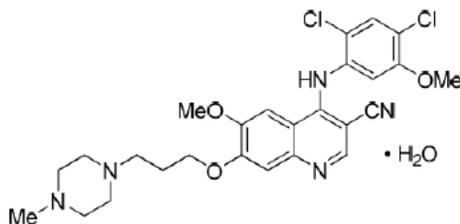
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

CMC Review Data Sheet

Chemical Structure	
Molecular Formula	C ₂₆ H ₂₉ Cl ₂ N ₅ O ₃ •H ₂ O
Molecular Weight	548.46 (monohydrate) 530.46 (anhydrous)
United States Adopted Name (USAN)	bosutinib monohydrate
Chemical Name	3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-, hydrate (1:1).
Chemical Abstracts Service (CAS) Registry Number	CAS-380843-75-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS	
(b) (4)	IV			(b) (4)	4	Adequate	28-Feb-2012	See sections 1.4.1 & 3.2.P.4.1
	IV			4	Adequate	28-Feb-2012	See sections 1.4.1 & 3.2.P.4.1	
	III			4	Adequate	28-Feb-2012	See sections 1.4.1 & 3.2.P.7	
	III			3 & 4	Adequate	17-Feb-2012	Reviewed by Dr. Xuhong Li	
	III			3 & 4	Adequate	17-Feb-2012	Reviewed by Dr. Xuhong Li	
	III			3 & 4	Adequate	16-Jun-2011	Reviewer by Dr. George Lunn	
	III			3 & 4	Adequate	11-Mar-2005 & 09-Sep-2003	Reviewed by Dr. Gene Holbert & Dr. Edwin Jao See sections 1.4.1 & 3.2.P.7	
	III			3 & 4	Adequate	23-Jun-2006	Reviewed by Josephine Jee See sections 3.2.P.2.4 & 3.2.P.7	

¹ Action codes for DMF Table:
1 – DMF Reviewed.

CMC Review Data Sheet

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
IND	68,268	Bosutinib (SKI-606)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10-May-2012	D. Smith
Pharm/Tox	Impurity limits in drug substance are acceptable	17-Jul-2012	Shwu Luan Lee
Biopharm	Acceptable	15-May-2012	Akm Khairuzzaman
LNC	N/A		
Methods Validation	Acceptable	04-May-2012	Daniel J Mans
DMEPA*	The proposed proprietary name, Bosulif is acceptable	03-Feb-2012	Kimberly De Fronzo
EA	Categorical exclusion accepted (see review)	09-Jul-2012	Joyce Crich
Microbiology	approval from microbiology product quality standpoint	12-Jun-2012	Robert Mello

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 203341

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application cannot be recommended for approval from a chemistry, manufacturing, and controls (CMC) standpoint until the following deficiency is satisfactorily resolved:

The post-approval stability commitment in Section P.8.2 is not adequate according to ICH Q1A(R2) Section II(B)(8).

The approvability and the granted expiration dating period for the drug product is pending on the resolution of the deficiency.

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

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance bosutinib is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

Bosutinib monohydrate is manufactured by [REDACTED] (b) (4)

[REDACTED] Detailed information regarding designation of the [REDACTED] (b) (4) starting materials, the commercial sources, acceptance criteria, and associated methods of analysis are provided.

A Quality by Design (QbD) approach was employed for the manufacturing process based on the principles of ICH Q8, Q9 and Q11, including quality target product profile (QTPP), identification of the potential critical quality attributes (CQAs), the process parameters (CPP, KPP) that have a potential impact on these CQAs, and operating spaces for each step of the drug substance manufacturing process by statistically designed multivariate experimental (DoEs) approaches, leading to the overall operating space and control strategy for the manufacturing process. The

CMC Assessment Section

quality attributes of bosutinib monohydrate are defined in the drug substance specification based on a traditional approach. The key and critical process parameters for each manufacturing step are provided, as well as the regulatory commitment for the operating range.

Bosutinib monohydrate is a white to yellowish tan powder. It is classified as a BCS Class 4 compound (low soluble and low permeable material) with pH dependent solubility. It is non-hygroscopic. The selected polymorph form (b) (4) of bosutinib monohydrate for development and commercialization is the (b) (4)

The submitted stability data support the proposed retest period of (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

(2) Drug Product

Bosulif[®] (bosutinib) tablets are available in 100 mg and 500 mg dosage strengths. The tablets contain bosutinib monohydrate as the active pharmaceutical ingredient equivalent to 100 mg and 500 mg of bosutinib anhydrous together with microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow (for 100 mg tablet) and iron oxide red (for 500 mg tablet).

Bosulif[®] (bosutinib) tablets are available for oral administration in two strengths: a 100 mg yellow, oval-shaped, biconvex, immediate release film coated tablet with debossed with "Pfizer" on one side and "100" on the other; Bosutinib film coated tablets, a 500 mg red, oval-shaped, biconvex immediate release film coated tablet with "Pfizer" on one side and "500" on the other. Bosulif[®] (bosutinib) tablets are supplied in 60 ml HDPE bottles of 120 tablets for 100 mg strength and of 30 tablets for 500 mg strength.

The applicant submitted the stability data from three primary batches for the 100 mg strength and 500 mg strength tablets up to 24 months at 25°C/60% RH and 30°C/75% RH, and up to 6months at 40°C/75% RH in the primary stability container closure

CMC Assessment Section

system. Those stability data support the proposed 24 months shelf-life for the drug product in both strengths packaged in HDPE bottles and stored at controlled room temperature. Additionally, the submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

The NDA submission did not include any stability data for the proposed commercial container closure system which is different from the primary stability container closure system (e.g. configuration, fill volume, headspace, MVTR, and amount of desiccant). According to ONDQA's Initial Quality Assessment and Filling Review for this NDA dated 21-Dec-2011 in DARRTS, the issue of lacking stability data for the proposed commercial container closure system was determined as a review issue. During this review cycle, instead of providing any stability data for the proposed commercial container closure system after Agency's information request for such data, the applicant provided the calculations for moisture absorption capacity of desiccant canister and total available moisture within the commercial container closure system to justify the proposed shelf life in the proposed commercial container closure system. The provided justification appears to be reasonable, but it does not completely exclude possible impact on quality attributes linked to water content due to the potential difference in moisture level control. Although the risk of changing container closure system for solid dosage form is relatively small, the provided theoretical calculation of moisture exposure (MVTR vs desiccant capacity) is only a supporting data for moisture-barrier equivalence, and is not a replacement for stability study result from the proposed container closure system. According to ICH Q1A(R2) Section II(B)(4), Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Therefore, it is recommended that the Postapproval Stability Commitment be revised to include accelerated studies for 6 months along with the long-term studies through the proposed shelf life for the first three production batches of bosutinib 100 mg and 500 mg tablets, to monitor the stability trend and to confirm the shelf life, based on ICH Q1A(R2) Section II(B)(8) (refer to the Letter of Information Request dated 18-Jul-2012). The approvability of the drug product bosutinib 100 mg and 500 mg strength tablets packaged in the proposed commercial container closure system is pending the applicant's response to this deficiency.

The recommendation and conclusion on the approvability for this NDA were made by incorporating QBD principle, risk management, and scientific rationale based on the stability data from the primary stability study container closure system, provided that if the firm agrees to revise the Postapproval Stability Commitment [refer ICH Q1A(R2) II(B)(8)] to monitor the stability of marketed drug products in the proposed commercial container closure system. The CMC reviewer does not think this special situation (with very low risk to product quality under the circumstance of lacking stability data for the proposed commercial container closure system at filing was determined as a review issue) should be viewed as a precedent in general for any future NDA or ANDA submission as any scenario of container closure system varies from each other and very much depends on the nature of drug product.

CMC Assessment Section

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

Bosulif[®] (bosutinib) Tablets are indicated for the treatment of chronic, accelerated, or blast phase Ph⁺ chronic myelogenous leukemia (CML) in adult patients with resistance, or intolerance to prior therapy.

Bosulif[®] (bosutinib) Tablets are dosed orally with food. The recommended dose and schedule of Bosulif is 500 mg once daily. Dose adjustments may be required for hematologic and non-hematologic adverse reactions.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has not responded to the deficiency requesting a revision to the post-approval stability commitment in Section P.8.2 which is the basis for a Not-Approval Recommendation.

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Bosulif.

Methods validation was completed on 04-May-2012 by the FDA St. Louis Laboratory for the drug substance and drug product analysis which are confirmed to be acceptable for quality control and regulatory purposes. Note: it is not required for approval of the NDA.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 10-Jul-2012 are acceptable from the CMC perspective.

The Office of Compliance issued an overall “acceptable” recommendation dated 10-May-2012 for all facilities used for manufacturing and control of the drug substance and drug product.

CMC Assessment Section

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

(See appended electronic signature page)

Joyce Crich, Ph.D, Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Debasis Ghosh, Ph.D., Acting CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Janice Brown, Ph.D., Acting Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

JOYCE Z CRICH
07/20/2012

JANICE T BROWN
07/20/2012



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) 539-2158

Date: May 4, 2012
To: Joyce Crich, CMC Reviewer
Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)
From: Daniel J. Mans, Chemist (HFD-920)
Subject: Methods Validation for NDA 203341
Bosulif (Bosutinib monohydrate) 100 mg tablets
Pfizer, Inc.

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

1. Assay and identification of bosutinib monohydrate by high-performance liquid chromatography (Pfizer, :08001).
2. Determination of degradation products of bosutinib 100 mg and 500 mg tablets by high performance chromatography (Pfizer TM-01-0797A).

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods.

1. Determination of degradation products of bosutinib 100 mg and 500 mg tablets by high performance chromatography (Pfizer TM-01-0797A).
 - On page 1, under Solution Preparation, (b) (4).
 - On page 4 Table 5 lists approximate RRT's for identified process related impurities and degradation products but does not identify them specifically as process related or degradation product. The specification states that the limit is (b) (4) for individual degradation products and (b) (4) for total degradation products. As written, the analyst can not determine which compounds are degradation products and which are process related impurities; therefore the applicant should identify these along with the RRTS's. A specification for process related impurities is also needed for the Bosulif tablet.

Summary of Results

NDA 203202

1. Assay and identification of bosutinib monohydrate by high-performance liquid chromatography (Pfizer, :08001).

<u>Test</u>	<u>Found</u>	<u>Specification</u>	
ID	RRT 1.00	(b) (4)	passes
Assay	(b) (4)	(b) (4)	passes

3. Determination of degradation products of bosutinib 100 mg and 500 mg tablets by high performance chromatography (Pfizer TM-01-0797A).

	<u>Found</u>	<u>Limit</u>
Bosutinib drug product (100 mg) impurities		
Individual degradation impurities		(b) (4)
Total degradation impurities		

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/s/

MICHAEL L TREHY
05/07/2012

BENJAMIN J WESTENBERGER
05/07/2012

Date: 06-Jan-2012

To: NDA 203341

From: Joyce Crich, Ph.D. Product Quality Reviewer, Div 1, Br II, ONDQA

Through: Sarah Pope Miksinski, Ph.D. Branch Chief, Div 1, Br II, ONDQA

Subject: PQMM-DS (Product Quality and Manufacturing Memo for Drug Substance)

Purpose:

The purpose of this memo is to provide a brief overview of the manufacturing process for drug substance bosutinib monohydrate and a brief summary of QbD approaches including risk control strategy as proposed in the submission.

This memo is intended to provide the drug substance reviewer's preliminary risk assessment and suggested considerations for pre-approval inspection. It is not intended to provide inspectional instructions.

Background:

The application (NDA 203341) was submitted on 17-Nov-2011 under 505(b)(1) by Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer, Inc.) for the commercialization of bosutinib monohydrate (film coated tablet, 100 mg and 500 mg), a new molecular entity (NME), as a treatment for chronic, accelerated, or blast phase Ph+ Chronic Myelogenous Leukemia (CML) in adult patients with resistance or intolerance to prior therapy. The application has been granted a "Standard" review status.

Drug Substance Summary of Manufacturing:

[Redacted text block with (b) (4) notation]

. The applicant employed a Quality by Design (QbD) approach for the manufacturing process based on the principles of ICH Q8 and Q9.

QbD Approaches and Control Strategies (manufacturing):

The Applicant's Quality by Design approach contains: quality target product profile (QTPP), identification of the potential critical quality attributes (CQAs), the process parameters (CPP, KPP) that have a potential impact on these CQAs, and operating spaces for each step of the drug substance manufacturing process by statistically designed multivariate experimental (DoEs) approaches, leading to the overall operating space for the manufacturing process.

The quality attributes of bosutinib monohydrate are defined in the drug substance specification (see Appendix II), refer to Reviewer's Preliminary Assessment of Risk (see Pages 3-4). The specification is based on a traditional approach, and no real-time release testing (RTRT) is proposed for any of the quality attributes listed in the specification. Although [Redacted] (b) (4) was used in the manufacturing process, it was not included in the drug substance specification as a separate test. However, the applicant proposed a test for [Redacted] (b) (4) at release.

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/s/

JOYCE Z CRICH
02/02/2012

DEBASIS GHOSH
02/02/2012

SARAH P MIKSINSKI
02/06/2012

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

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Joyce Crich, CMC Reviewer
Akm Khairuzzaman, Biopharm Review
Janice Brown, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: joyce.crich@fda.hhs.gov; Akm.Khairuzzaman@fda.hhs.gov
Phone: (301)-301-796-3882; 301-796-3886
Fax.: (301)-CMC Reviewer's FAX number

Through: Sarah Pope Miksinski, Chief Branch 2
Phone: (301)-796-1436

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203341

Name of Product: bosutinib monohydrate

Applicant: Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer, Inc.)

Applicant's Contact Person: Carl DeJuliis, Pharm.D.

Address: 500 Arcola Road, Collegeville, PA 19426-3982

Telephone: (860) 441-1693 Fax:

Date NDA Received by CDER: **11/17/2011**
NME

Submission Classification/Chemical Class:

Date of Amendment(s) containing the MVP:

Special Handling Required: No

DATE of Request: **December 12, 2011**

DEA Class: N/A

Requested Completion Date: **3/30/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **9/17/2012**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

Appears This Way On Original

MVP Reference #	METHODS VALIDATION REQUEST			NDA # (b) (4)
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
08001	DS - ASSAY and Identity	3.2.S.4.3	0	
TM-0797A	Determination of Degradation Products of Bosutinib 100 mg and 500 mg Tablets by High Performance Liquid Chromatography	3.2.P.5.3	0	
			0	
Additional Comments:				

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

JANICE T BROWN
12/20/2011

SARAH P MIKSINSKI
12/21/2011

JEANNIE C DAVID
12/21/2011
ONDQA Methods Validation Project Manager

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

NDA Number: 203341 **Supplement Number and Type:** **Established/Proper Name:** bosutinib tablets

Applicant: Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer, Inc.) **Letter Date:** 17-Nov-2011 **Stamp Date:** 17-Nov-2011

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?	X		

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.			N.A.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW 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) 	X		
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) 	X		

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

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) 	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 or Supplement (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 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?	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	
	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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

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

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

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

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

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

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

CMC IR – 74 day letter: Submit available long term and accelerated stability data for bosutinib drug product batches intended for commercialization.

{See appended electronic signature page}

Janice Brown, Branch II/DNDQA1/ONDQA

12-Dec-2011

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D. /DNDQA1/ONDQA
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02-Dec-2011

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/s/

JANICE T BROWN
12/20/2011

SARAH P MIKSINSKI
12/21/2011

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

OND Division: Division of Hematology Products
NDA: 203341 (IND 68,268)
Applicant: Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer, Inc.)
Stamp Date: 17-Nov-2011
PDUFA Date: 17-Sep-2012 (Standard)
Proprietary (Brand) Name of Drug Product: BOSULIF®
Established Name: bosutinib monohydrate
Dosage Form(s): Film Coated Tablet
Strength(s): 100 mg, 500 mg
Route of Administration: Oral
Proposed Indication(s): For the treatment of chronic, accelerated, or blast phase Ph+ Chronic Myelogenous Leukemia (CML) in adult patients with resistance or intolerance to prior therapy
CMC Lead: Janice Brown, Branch II/DNDQA1/ONDQA
Chief, Branch II: Sarah Pope Miksinski/DNDQA1/ONDQA
Review team recommendation: Team review
 CMC reviewer: Joyce Crich
 Biopharmaceutics reviewer: Akm Khairuzzaman

	Yes	No
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	X	<input type="checkbox"/> (see below)

1. Submit available long term and accelerated stability data for bosutinib drug product batches intended for commercialization.

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
CDRH	Not Applicable
EA	Categorical exclusion requested
EES	Inspection request was submitted on 22-Nov-2011
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	See methods validation request in DARRTS
Microbiology	Reviewer requested
Pharm-Tox	To be determined by primary reviewer
Statistics	N/A

SUMMARY

CML is caused by a reciprocal translocation between the long arms of chromosomes 9 and 22. The translocation results in the production of a Bcr-Abl oncoprotein, which exhibits constitutive tyrosine kinase activity. Bosutinib, a substituted 4-anilinoquinolone-3-carbonitrile, is a selective tyrosine kinase inhibitor (TKI) inhibitor that inhibits the abnormal Bcr-Abl tyrosine kinase that promotes chronic myelogenous leukemia. BOSULIF is indicated for the treatment of chronic, accelerated, or blast phase Ph⁺ chronic myelogenous leukemia (CML) in adult patients with resistance, or intolerance to prior therapy. The recommended starting oral dose of bosutinib tablets is 500 mg by mouth once daily. Bosutinib tablets should be taken with food.

BOSULIF (bosutinib monohydrate) tablets are supplied in two strengths: a 100 mg yellow film-coated tablet and 500 mg red film-coated tablet. Both strengths (b) (4) are differentiated by size, color and debossing. Each BOSULIF tablet contains either 103.40 mg of bosutinib monohydrate (equivalent to 100 mg of bosutinib) or 516.98 mg of bosutinib monohydrate (equivalent to 500 mg of bosutinib) and inactive ingredients microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow (for 100 mg tablet) and iron oxide red (for 500 mg tablet).

BACKGROUND

Phase 1 and 2 Capsule Formulations - A 50 mg and 100 mg capsule formulation using a (b) (4) was used in the Phase 1 and 2 clinical studies. (b) (4)

(b) (4). The sponsor changed the dosage form from a capsule to a tablet during phase 2. The tablet formulation used in the Phase 2 and Phase 3 CML studies (200-WW and 3000- WW) is bioequivalent to the capsule formulation used in early Phase 1 and 2 studies (100-US and 200-WW).

Phase 3 Tablet Formulation - Film coated 100 mg and 500 mg tablets (b) (4) were developed for use in the Phase 3 clinical study. Changes were made to the formulation to (b) (4). A BE study showed that the 100-mg tablet formulation used in the Phase 2 and Phase 3 CML studies (200-WW and 3000-WW) is bioequivalent to the proposed commercial formulation.

Commercial Formulation – The tablet formulation used in the phase 3 study differs from the commercial formulation in the following ways:

- (b) (4)
-
-
-

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/s/

JANICE T BROWN
12/20/2011

DEBASIS GHOSH
12/20/2011

SARAH P MIKSINSKI
12/21/2011