

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202570Orig1s000**

**CHEMISTRY REVIEW(S)**

ONDQA Division Director's Memo  
NDA 202570, XALKORI (crizotinib) Capsules, 200 and 250 mg  
Date: 04-AUG-2011

## **Introduction**

XALKORI (crizotinib) capsules are hard gelatin capsules supplied in two strengths (200 mg and 250 mg). A (b) (4) is used for capsule filling, and all excipients are compendial. The 200 mg capsules will be provided as white opaque/pink opaque hard gelatin capsules with "CRZ 200" printed on the body and "Pfizer" printed on the cap. The 250 mg strength capsules will be provided as pink opaque/pink opaque hard gelatin capsules with "CRZ 250" and "Pfizer" printed on body and cap, respectively. Both will be packaged in HDPE bottles with child-resistant caps (60 count/bottle).

XALKORI capsules are proposed for treatment of Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). The recommended dose is 250 mg twice daily, with or without food. The capsules should be swallowed whole.

"XALKORI" was confirmed as a conditionally acceptable trade name in a 23-JUN-2011 review by the Division of Medication Errors Prevention and Analysis (DMEPA). The proposed trade name was confirmed as acceptable in an updated 03-AUG-2011 DMEPA review.

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

## **Administrative**

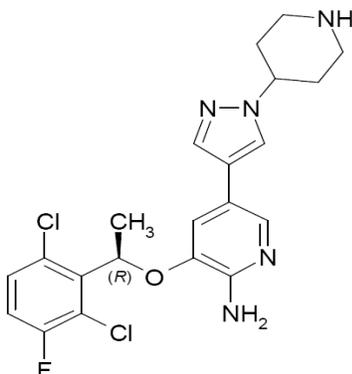
The original submission of this 505(b)(1) NDA was received 30-MAR-2011 from Pfizer, Inc. (San Diego, CA). Three (3) solicited CMC amendments were also reviewed during the review cycle. The Chemistry, Manufacturing and Controls assessment is captured in the following reviews, respectively: Chemistry Review #1 for both drug substance and drug product (dated 03-AUG-2011 and 02-AUG-2011, respectively), Chemistry Review for Analytical Methodology (02-AUG-2011), Biopharmaceutics Review #1 (dated 26-JUL-2011), and Biostatistics Review (dated 27-JUL-2011).

The NDA is supported by IND 73,544 and ten (10) drug master files (DMFs). Primary CMC reviews for both drug substance and drug product, as well as biopharmaceutics, confirm an approval recommendation, and all primary reviews confirm that there are no outstanding CMC deficiencies. An acceptable overall recommendation from the Office of Compliance was provided on 03-AUG-2011. Supportive reviews of analytical methodology (Dr. R. Lu, review dated 02-AUG-2011) and biostatistics (Dr. M. Shen, review dated 27-JUL-2011) capture the assessment of application-specific Quality by Design (QbD) elements. The supportive reviews also confirm that there are no outstanding CMC deficiencies that would impact approvability.

**This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.**

## Drug Substance (Crizotinib)

Chemical Name: (R)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]pyridin-2-amine



Crizotinib is a new molecular entity. It is a non-hygroscopic, white to pale yellow powder and insoluble in water. It possesses pKa values of 9.4 and 5.6, and it is highly soluble in acidic pH. Several polymorphic forms are possible, with (b) (4) as the most stable and as proposed for commercialization. The crizotinib structure contains one chiral center; (b) (4)

### Crizotinib

The Applicant proposed a Quality by Design (QbD) approach to optimize the reaction conditions. This approach included the risk assessment, identification of critical quality attributes (CQA), material attributes (MA), critical and non-critical process parameters (CPP, NCPP), design space, control strategies, and change management.

The Applicant also proposed an Analytical Target Profile (ATP, HPLC method TM- (b) (4) for assay and related substances) as part of the employed QbD approach. Based on evaluation of this element, the Agency determined that further discussions regarding the proposed ATP are needed before an approval recommendation can be made. The Applicant subsequently decided to withdraw the proposed ATP from the application.

The proposed **re-test period of (b) (4) months** when stored at the recommended container closure system at ambient storage conditions is granted.

## Drug Product (Crizotinib Capsules, 200 and 250 mg)

The drug product is manufactured (b) (4)

All excipients used in the formulation are compendial and are conventional for solid oral dosage forms.

The Applicant employed a risk-based, QbD approach to the development of crizotinib capsules. The Applicant defined a quality target product profile (QTPP) along with critical quality

attributes (CQAs) for the drug product. DOE and risk assessment processes used throughout development defined the investigations performed to gain a thorough understanding of product quality. The investigations covered a wide range of input and material attributes as well as process parameters and led to a clear understanding of the relationships between, and impact of, the parameters investigated on the CQAs. The Applicant used this understanding to propose a design space that ensures delivery of drug product that consistently meets the required quality. The Applicant proposed a Method Operable Design Region (MODR) for the HPLC method TM-<sup>(b) (4)</sup> (identity, assay, impurities in drug product). This QbD element is approved as part of this application; it essentially mirrors USP criteria for chromatographic method adjustments. Specific reference is also made to the supporting review by the Office of Biostatistics (Dr. M Shen), which evaluated the statistical rationale used for the Applicant's DOE studies and supporting statistical information related to the proposed MODR.

The commercial packaging is 60-count HDPE bottles. The Applicant proposed a <sup>(b) (4)</sup> 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 fifteen (15) month expiry for the drug product, as packaged in the commercial configuration and when stored at USP controlled room temperature.**

**Please include the drug product expiry in the action letter.**

Thank you,

Richard (Rik) Lostritto, Ph.D., Director  
ONDQA, Division-I

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/s/  
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RICHARD T LOSTRITTO  
08/04/2011



**NDA 202-570**

**XALKORI™ (crizotinib) Capsules**

**(200 mg and 250 mg)**

**Pfizer, Inc.**

**Zedong Dong, Ph.D.**

**Product Quality Reviewer  
DRUG PRODUCT**

**Office of New Drug Quality Assessment, Division I**

**CMC REVIEW OF NDA 202570 DRUG PRODUCT**

**For the Division of Drug Oncology Products (HFD-150)**

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# Chemistry Review Data Sheet

1. NDA 202-570
2. REVIEW #: 1
3. REVIEW DATE: August 2, 2011
4. REVIEWER: Zedong Dong, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 73544 submission	12/12/ 2005
Original IND 73544 CMC review by Ying Wang	02/10/2006
CMC only pre-NDA meeting	10/29/2010
Pre-NDA Meeting Minutes	11/12/2010

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

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission 0002	03/30/2011
Amendment 0021 (Drug Product 9-Month Stability)	06/29/2011
Amendment 0028 (Labeling)	07/13/2011
Amendment 0029 (Response to CMC IR)	07/20/2011
Amendment 0033 (Response to CMC IR)	07/27/2011
Amendment 0035 (Response to CMC IR)	07/29/2011

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.  
Address: 10646 Science Center Drive  
San Diego, CA 92121

## Chemistry Review Data Sheet

Representative: Ron Domingo  
Telephone: (858) 622-3234

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: XALKORI™
- b) Non-Proprietary Name (USAN): Crizotinib
- c) Code Name/# (ONDC only): PF-02341066
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: P

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

10. PHARMACOL. CATEGORY: ALK-positive advanced non-small cell lung cancer (NSCLC)

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 200 mg and 250 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

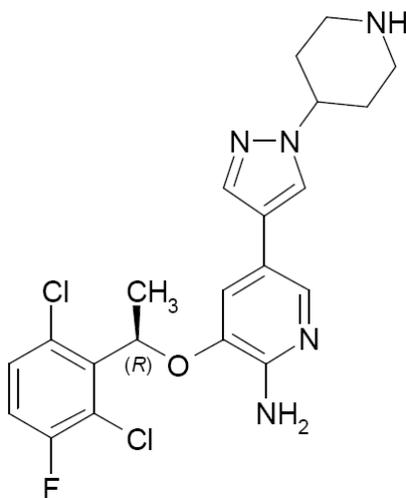
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Chemical Names:**

IUPAC: (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine

CAS: 3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(4-piperidinyl)-1*H*-pyrazol-4-yl]-2-pyridinamine

## Chemistry Review Data Sheet

**Molecular Formula:** C<sub>21</sub>H<sub>22</sub>Cl<sub>2</sub>FN<sub>5</sub>O**Molecular Weight:** 450.34 Daltons

Crizotinib

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	06/09/2010	By Dr. Deepika Arora in NDA 22-368
	IV			3	Adequate	10/29/2010	By Dr. Sharon Kelly
	III			4	N/A	N/A	N/A
	III			3	Adequate	07/07/2010	By Dr. Caroline Strasinger
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A
	III			3	Adequate	06/23/2006	By Dr. Josephine Jee

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is adequate data in the application, therefore the DMF was not reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	See body of text	7/27/2011	Meiyu Shen
EES	Pending		Shawn Gould
Pharm/Tox	N/A		
Biopharm	Approval	07/26/2011	Kareen Riviere
Analytical	Approval	08/02/2011	Donghao (Robert) Lu
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	N/A		
EA	Category exclusion (see review)		



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

Microbiology	Approval	08/01/2011	Stephen Langille
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# The Chemistry Review for NDA 202-570

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 202-570 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending satisfactory resolution of the Labeling and EES issues.

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

N/A

### II. Summary of Chemistry Assessments

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

##### Drug Product:

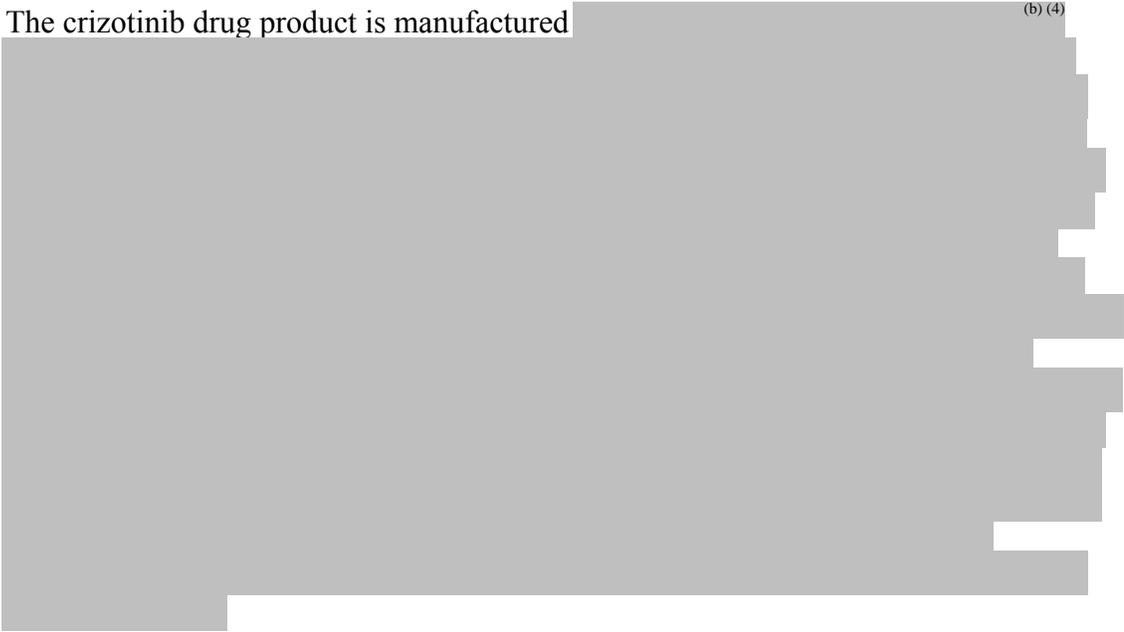
The commercial crizotinib drug product is a hard gelatin capsule formulation in two strengths (200 mg and 250 mg), with a (b)(4) being used for capsule filling. The excipients (including the components in gelatin capsule shell and printing ink) used for manufacturing the drug product are all compendial grade. Crizotinib capsules 200 mg will be provided as white opaque/pink opaque hard gelatin capsules with “CRZ 200” printed on the body and “Pfizer” printed on the cap. The 250 mg strength will be provided as pink opaque/pink opaque hard gelatin capsules with “CRZ 250” and “Pfizer” printed on body and cap, respectively. The drug product will be packaged in HDPE bottles with child-resistant caps (60 counts/bottle).

Three formulations (powder in capsule (PIC), immediate release tablet, and intravenous solution) were used in clinical trials prior to the commercial capsule. The PIC formulation (10 mg, 50 mg, and 100 mg) was used for early stage Phase I studies. The immediate release tablet (50 mg and 100 mg) formulation, with (b)(4) drug loading, was later developed to meet the increased demand for further clinical trials. However, due to the lower drug loading of the tablet, the commercial capsule formulation was developed for administration convenience. The tablets and capsules use qualitatively similar excipients. The IV solution was developed for use in the absolute bioavailability study.

## Executive Summary Section

The crizotinib drug product is manufactured

(b) (4)



(b) (4)



Satisfactory batch analysis results were provided for one registration batch of 200 mg strength (batch# 9806533000) and three registration batches of 250 mg strength (batch# 9806683000, 9806633000, and 9806683001).

Nine-month stability results for the registration batches were submitted for storage under 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH for the proposed commercial packaging configurations.

(b) (4)



Based on the stability results, the

## Executive Summary Section

recommended expiry for the crizotinib drug product is fifteen months. The applicant commits to placing the first three commercial scale batches of drug product on stability to confirm shelf life. In addition, annual production batches will be selected for stability testing at a rate of at least one batch per year per strength per packaging configuration according to the submitted post-approval stability protocol.

Per Dr. Donghao Lu's review on analytical methods and validation, the proposed commitment on Analytical Target Profile (ATP) is withdrawn from the application. The proposed Method Operable Design Regions (MODR) for the HPLC methods TM- (b) (4) (for identity, assay and impurities in drug product) and TM- (b) (4) (for assay and impurities in drug substance) are acceptable.

Immediate container labeling was submitted for the 60 counts/bottle packaging configuration, which appears acceptable.

Claim for category exclusion is granted per 21 CFR Part 25.31 (b).

**Drug Substance:**  
(reproduced from Dr. Debasis Ghosh's Review)

Crizotinib, the drug substance, is a New Molecular Entity (NME). It is an inhibitor of ALK receptor tyrosine kinase. It is indicated for the treatment of ALK positive advanced non-small cell lung cancer (NSCLC). It is a non-hygroscopic, white to pale yellow powder and insoluble in water. It has pKa values of 9.4 and 5.6 and it is highly soluble in acidic pH. Several polymorphic forms are possible. However, the (b) (4) is stable and it is the proposed commercial form. It has one chiral center and (b) (4). Its structure was elucidated by IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, MS, UV/Vis, optical rotation and X-ray crystallography.

Crizotinib (b) (4). The applicant proposed a Quality by Design (QbD) approach to optimize the reaction conditions. The QbD approach led to the risk assessment, identification of critical quality attributes (CQA), material attributes (MA), critical and non-critical process parameters (CPP, NCPP), design space, control strategies, and change management. The applicant used the principles of ICHQ8, Q9 and Q10 to develop QbD approach.

To assure the identity, strength, purity, and quality, the crizotinib is controlled by the acceptance criteria of quality attributes including identification, assay, impurities, and particle size. Stability studies with crizotinib indicate that it is sensitive to strong acid, strong base, intense light and oxidation conditions. However, the related substance impurity and degradation products are well controlled by specification. The applicant proposed a retest period of (b) (4) months. Based on the principles of ICHQ1E and the risk

## Executive Summary Section

assessment, the retest period of (b) (4) months at long-term storage condition (25°C/60%RH) is granted at this time.

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

Crizotinib capsules are available in 200 mg and 250 mg strengths in 60 counts/bottle packaging configuration. The capsules are recommended to be stored at 25°C (77°F), with excursions permitted to 15°C - 30°C (59°F - 86°F). A fifteen-month expiry at the proposed storage conditions will be granted based on the provided stability data. This is to be communicated to the applicant in the action letter.

**C. Basis for Approvability or Not-Approval Recommendation** (*Harmonized with DS review*)

This new drug application (202-570) is recommended to be approved from the CMC perspective pending an overall recommendation of the cGMP status of the manufacturing and testing facilities from the Office of Compliance. The recommendation for approval is based upon the acceptable identity, strength, quality, and purity upon the evaluation of the drug substance and drug product.

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

*(see appended electronic signature page)*

Zedong Dong, Ph.D.  
Chemistry Reviewer  
Division I, ONDQA

**B. Endorsement Block**

*(see appended electronic signature page)*

Sarah Pope Miksinski, Ph.D.,  
Branch Chief  
Branch II, Division I, ONDQA

Rik Lostritto, Ph.D.  
Division Director  
Division I, ONDQA

**C. CC Block: entered electronically in DARRTS**

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ZEDONG DONG  
08/02/2011

RICHARD T LOSTRITTO  
08/02/2011

**Crizotinib  
Capsule  
200 mg and 250 mg**

**Pfizer Inc.**

**CMC Reviewer  
(Analytical sections)**

**Donghao (Robert) Lu, Ph.D.**

**Division I of Pre-Marketing Assessment  
Office of New Drug Quality Assessment**

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DONGHAO R LU  
08/02/2011

RICHARD T LOSTRITTO  
08/02/2011

# **NDA 202570**

**Xalkori™  
(crizotinib) Capsules  
200 mg & 250 mg**

**Pfizer, Inc.**

**Debasis Ghosh, M. Pharm., Ph.D.**

**Product Quality Reviewer  
DRUG SUBSTANCE**

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

**CMC REVIEW OF NDA 202570 DRUG SUBSTANCE  
For the Division of Drug Oncology Products (HFD-150)**

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CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 202-570
2. REVIEW #: 1
3. REVIEW DATE: 01-Aug-2011
4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 73544 submission	12-Dec-2005
Original IND 73544 CMC review by Ying Wang	10-Feb-2006
CMC only pre-NDA meeting	29-Oct-2010
Pre-NDA Meeting Minutes	12-Nov-2010

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

Submission(s) Reviewed	Serial Number	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	SR 002	SD 004	30-Mar-2011	30-Mar-2011
Drug Product 9 month Stability	SR 021	SD 022	29-Jun-2011	30-Jun-2011
Response to FDA Request for Information on 06-Jul-2011	SR 026	SD 027	12-Jul-2011	12-Jul-2011
Labeling Amendment*	SR 027	SD 028	13-Jul-2011	13-Jul-2011
Response to FDA Request for Information on 11-Jul-2011 and 12-Jul-2011*	SR 028	SD 029	13-Jul-2011	13-Jul-2011
Follow up to Response to FDA Request for Information on 06-Jul-2011*	SR 030	SD 030	15-Jul-2011	15-Jul-2011
Responses to queries received on July 6, 8, and 12, 2011	SR 029	SD 031	20-Jul-2011	20-Jul-2011
Responses to queries received on July 25 and 26, 2011	SD 033	SD 034	28-Jul-2011	28-Jul-2011
Responses to queries received on July 25 and 26, 2011	SD 035	SD 035	29-Jul-2011	29-Jul-2011

\*not reviewed by Drug Substance Reviewer

## CMC Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Pfizer Inc  
Address: 10646 Science Center Drive  
San Diego, CA 92121  
Representative: Ron Domingo  
Manager Worldwide Regulatory Strategy  
Telephone: (858) 622-3234

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: XALKORI™
- b) Non-Proprietary Name: Crizotinib
- c) Code Name/# (ONDQA only): NA
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1 New Molecular Entity
  - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Anti-cancer

11. DOSAGE FORM: Capsule

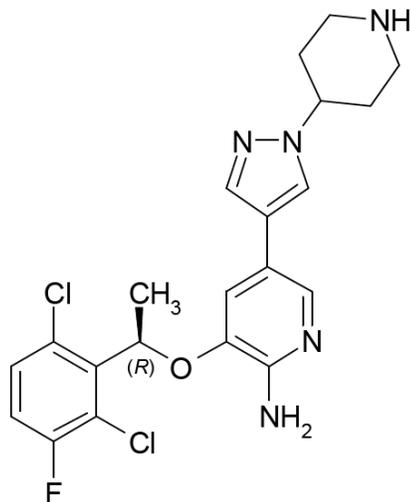
12. STRENGTH/POTENCY: 200 mg and 250 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

## CMC Review Data Sheet

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

**Molecular Formula** $C_{21}H_{22}Cl_2FN_5O$ **Molecular Weight**

450.34 Daltons

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

- [No DMF for Drug Substance](#)
- [See Drug Product Review by Dr. Zedong Dong](#)

**B. Other Documents:**

NA

CMC Review Data Sheet

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biostatistics	See Review Comments	27-Jul-2011	Meiyu Shen
EES	Pending as of the date of this review		Shawn Gould & Michele Perry Williams
Analytical	Approval	02-Aug-2011	Donghao (Robert) Liu
Pharm/Tox	Pending as of the date of this review		Brenda Gehrke
Biopharm	Approval	26-Jul-2011	Kareen Riviere
LNC	N/A	N/A	N/A
Methods Validation	N/A, according to the current ONDQA policy	N/A	N/A
DMEPA*	<ul style="list-style-type: none"> <li>• Initial Review</li> <li>• Final Review Pending as of the date of this review</li> </ul>	<ul style="list-style-type: none"> <li>• 26-Jul-2011</li> </ul>	Kimberly A Defronzo
EA	Categorical exclusion (see DP review by Dr. Zedong Dong)	N/A	N/A
Microbiology	Approval	01-Aug-2011	Stephen Langille

## Executive Summary Section

# The CMC Review for NDA 202-570

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 202-570 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending satisfactory resolution of the Labeling and EES issues.

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

None

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

Crizotinib, the drug substance, is a New Molecular Entity (NME). It is an inhibitor of ALK receptor tyrosine kinase. It is indicated for the treatment of ALK positive advanced non-small cell lung cancer (NSCLC). It is a non-hygroscopic, white to pale yellow powder and insoluble in water. It has pKa values of 9.4 and 5.6 and it is highly soluble in acidic pH. Several polymorphic forms are possible. However, the (b) (4) is stable and it is the proposed commercial form. It has one chiral center and (b) (4). Its structure was elucidated by IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, MS, UV/Vis, optical rotation and X-ray crystallography.

Crizotinib (b) (4)

The applicant proposed a Quality by Design (QbD) approach to optimize the reaction conditions. The QbD approach led to the risk assessment, identification of critical quality attributes (CQA), material attributes (MA), critical and non-critical process parameters (CPP, NCPP), design space, control strategies, and change management. The applicant used the principles of ICHQ8, Q9 and Q10 to develop the QbD approach.

To assure the identity, strength, purity, and quality, the crizotinib is controlled by the acceptance criteria of quality attributes including identification, assay, impurities, and particle size. Stability study with crizotinib indicates that it is sensitive to strong acid, strong base, intense light and oxidation conditions. However, the related substance impurity and degradation products are well controlled by specification. The applicant proposed a retest period of (b) (4) months. **Based on the**

Executive Summary Section

principles of ICHQ1E and the risk assessment, the retest period of (b) (4) months at long-term storage condition (25°C/60%RH) is granted at this time.

**(2) Drug Product** (*reproduced from Dr. Zedong Dong’s Review of Drug Product*)

“The commercial crizotinib drug product is a hard gelatin capsule formulation in two strengths (200 mg and 250 mg), with a (b) (4) being used for capsule filling. The excipients (including the components in gelatin capsule shell and printing ink) used for manufacturing the drug product are all compendial grade. Crizotinib capsules 200 mg will be provided as white opaque/pink opaque hard gelatin capsules with “CRZ 200” printed on the body and “Pfizer” printed on the cap. The 250 mg strength will be provided as pink opaque/pink opaque hard gelatin capsules with “CRZ 250” and “Pfizer” printed on body and cap, respectively. The drug product will be packaged in HDPE bottles with child-resistant caps (60 counts/bottle).

Three formulations (powder in capsule (PIC), immediate release tablet, and intravenous solution) were used in clinical trials prior to the commercial capsule. The PIC formulation (10 mg, 50 mg, and 100 mg) was used for early stage Phase I studies. The immediate release tablet (50 mg and 100 mg) formulation, with (b) (4) drug loading, was later developed to meet the increased demand for further clinical trials. However, due to the lower drug loading of the tablet, the commercial capsule formulation was developed for administration convenience. The tablets and capsules use qualitatively similar excipients. The IV solution was developed for use in the absolute bioavailability study.

The crizotinib drug product is manufactured (b) (4)

[Redacted text block]

[Redacted text block]

## Executive Summary Section

(b) (4) Satisfactory batch analysis results were provided for one registration batch of 200 mg strength (batch# 9806533000) and three registration batches of 250 mg strength (batch# 9806683000, 9806633000, and 9806683001).

Nine-month stability results for the registration batches were submitted for storage under 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH for the proposed commercial packaging configurations. (b) (4)

Based on the stability results, the recommended expiry for the crizotinib drug product is fifteen months. The applicant commits to placing the first three commercial scale batches of drug product on stability to confirm shelf life. In addition, annual production batches will be selected for stability testing at a rate of at least one batch per year per strength per packaging configuration according to the submitted post-approval stability protocol.

Per Dr. Donghao Lu's review on analytical methods and validation, the statement on Analytical Target Profile (ATP) is withdrawn from the application. The proposed Method Operable Design Regions (MODR) for the HPLC methods TM (b) (4) (for identity, assay and impurities in drug product) and TM- (b) (4) (for assay and impurities in drug substance) are acceptable.

Immediate container labeling was submitted for the 60 counts/bottle packaging configuration, which appears acceptable.

Claim for category exclusion is granted per 21 CFR Part 25.31 (b)."

**B. Description of How the Drug Product is Intended to be Used** (*reproduced from Dr. Zedong Dong's Review of Drug Product*)

"Crizotinib capsules are available in 200 mg and 250 mg strengths in 60 counts/bottle packaging configuration. The capsules are recommended to be stored at 25°C (77°F), with excursions permitted to 15°C - 30°C (59°F - 86°F). A fifteen-month expiry at the proposed storage conditions will be granted based on the provided stability data. This is to be communicated to the applicant in the action letter."

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation** (*Harmonized with DP review*)

This new drug application (202-570) is recommended to be approved from the CMC perspective pending an overall recommendation of the cGMP status of the manufacturing and testing facilities from the Office of Compliance. The recommendation for approval is based upon the acceptable identity, strength, quality, and purity upon the evaluation of the drug substance and drug product.

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

(See appended electronic signature page)

Debasis Ghosh, M. Pharm., Ph.D.  
Product Reviewer  
Branch II, Division I, ONDQA  
CDER, FDA

**B. Endorsement Block:**

(See appended electronic signature page)

Sarah Pope Miksinski, Ph.D.  
Branch Chief  
Branch II, Division I, ONDQA  
CDER, FDA

**C. CC Block:** entered electronically in DARRTS

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/s/  
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DEBASIS GHOSH  
08/02/2011

SARAH P MIKSINSKI  
08/03/2011

**Date:** 26-May-2011

**To:** NDA 202570

**From:** Debasis Ghosh, Ph.D. Product Quality Reviewer, Div 1, Br II, ONDQA

**Through:** Sarah Pope, 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 summary of the drug substance manufacturing process and QbD approaches including risk control strategy as proposed in the submission. A brief description of analytical method validation using QbD approaches is also included.

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 202570) was submitted on 30-Mar-2011 under 505(b)(1) by Pfizer Inc for the commercialization of crizotinib, a new molecular entity (NME), as a treatment for NSCLC. The application has been granted "Priority" review status.

**Drug Substance Summary of Manufacturing:**

The manufacture and release of crizotinib are performed in Pfizer Ireland, Little Island site. Additional analytical testing sites are listed as Pfizer, Ringaskiddy, Ireland and Buttersworth, UK sites. The synthetic scheme is provided in Appendix I. Crizotinib is manufactured by (b) (4)

The applicant employed a Quality by Design (QbD) approach for the manufacturing process based on the principles of ICHQ8 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), risk and criticality assessment to understand the critical process parameters and how they influence CQAs, development of design space of the manufacturing process, and description of control strategies including monitoring of the product during the lifecycle.

The quality attributes of crizotinib are defined in the drug substance specification (see Appendix II). The specification is based on (b) (4) the quality attributes listed in the specification.

Based on the product knowledge, risk assessment and development studies, the firm identified **the following CQAs** and proposed control strategies to mitigate the risk:

(b) (4)



The Applicant provided the manufacturing design space and control strategy for the manufacturing process (See Appendix III).

**Reviewer's Preliminary Assessment of Risk (manufacturing):**



(b) (4)

**Considerations for Inspection (manufacturing):**



(b) (4)

**QbD Approach for Analytical Method Validation:**

The related substance impurities and drug substance assay are determined by a reverse-phase HPLC method (TM- (b) (4)). The method was developed based on the QbD principles incorporating risk and science based approach. While the method provides set point conditions for the operating parameters, the firm proposed flexibility based on the QbD approach.

The firm defined analytical target profile (ATP) as a guide to meet the intended purpose. Similar to design space in the manufacturing QbD, the firm proposes a concept of method operable design region (MODR) based on fractional factorial multivariate experimental design. Adjustment of operating variables within the proposed MODR is proposed to be handled via the internal quality system. The MODR and proposed post-approval changes for HPLC Method (TM (b) (4)) are provided in Appendix IV.

**Reviewer's Preliminary Assessment of Risk (Analytical):**

*The proposed ATP and MODR are part of the analytical validation approach. The flexibility of operating parameters within MODR is not yet evaluated. The proposed changes may influence the retention time as well as resolution of the analyte.*

**Consideration for Inspection (Analytical):**

- *Based on the method control strategy, the adherence to MODR and system suitability is essential to meet ATP.*

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DEBASIS GHOSH  
06/01/2011

SARAH P MIKSINSKI  
06/01/2011

**DATE:** May 25, 2011

**TO:** NDA 202-570 Crizotinib Capsules Inspection Team

**FROM:** Zedong Dong, Ph.D., 301-796-3885, zedong.dong@fda.hhs.gov (on behalf of the CMC review team)

**THROUGH:** Sarah Pope Miksinski, Ph.D.

**SUBJECT:** Product Quality Memo (PQM) for Crizotinib DP

***Introduction***

NDA 202-570 (Crizotinib) is submitted for the proposed indication of ALK-positive advanced NSCLC. This NDA is a rolling submission and has been granted a priority review designation. The memorandum is intended to assist the investigators with inspection preparation of crizotinib drug product and keep them informed of any elements that may benefit from additional attention from CMC-QbD perspective. This memo is not intended to provide inspectional instructions.

***Overall Summary of the Drug Product Manufacturing***

Two dose strengths (200 mg and 250 mg) are proposed for commercial marketing for the crizotinib capsules. Crizotinib capsule formulation contains no novel excipients (see composition in Appendix A). Both dose strengths of crizotinib capsules are manufactured using the same process (see Appendix B), (b) (4). Except for appearance, the proposed release specifications of quality attributes for both strengths of crizotinib capsules are identical (see specifications for 250 mg strength in Appendix C). (b) (4)

The concept of QbD is used in the formulation optimization and manufacturing process development of the drug product. The quality target product profile (QTPP) are described and linked to the proposed desired quality attributes. Based on the risk assessment and DOE results, key process parameters (KPP) and critical quality attributes (CQA) are determined and summarized in the crizotinib capsule design space (Appendix D).

***Overall Summary of Validation of HPLC Method (TM- (b) (4))***

The QbD concept is applied in the validation of TM (b) (4). The analytical target profile (ATP) of this method for assay and impurity testing is provided, which describes the analytical capability of the method. Risk assessment and DOE are used to determine the proposed method operable design region (MODR/Design Space) (b) (4)

(see MODR/Design Space in Appendix E).

***Reviewer's Assessment of Risk***

Based on the preliminary review of the application, the following risk items are identified:

(b) (4)

(b) (4)

3. With the incorporation of the QbD elements in both the DP manufacturing process and the validation of analytical method TM (b) (4), the applicant requests regulatory flexibility for changes within the design space/MODR. To ensure consistent product quality, a robust internal pharmaceutical quality system (PQS) is essential for the management of those changes.

APPENDIX A: Composition of Crizotinib Capsules, 200 mg and 250 mg

Name of Ingredients	Reference to Standards	Function	Unit Formula	
			200 mg Capsule	250 mg Capsule
<b>(b) (4) Composition</b>				
Crizotinib	Pfizer	Active	200.00 mg	250.00 mg
Colloidal Silicon Dioxide	NF/Ph Eur/JP			(b) (4)
Microcrystalline Cellulose	NF/Ph Eur/JP			
Anhydrous Dibasic Calcium Phosphate	USP/Ph Eur/JP			
Sodium Starch Glycolate	NF/Ph Eur/JP			
Magnesium Stearate <sup>a</sup>	NF/Ph Eur/JP			
(b) (4)				
(b) (4)				
<b>Capsule Shell<sup>b</sup></b>				
(b) (4)				(b) (4)
Gelatin	USP/Ph Eur/JP			(b) (4)
Titanium Dioxide	USP/Ph Eur			
(b) (4)				
Red Iron Oxide	USP/Ph Eur			
(b) (4)				(b) (4)
<b>Print Ink<sup>c</sup></b>				
(b) (4)				

HG is hard gelatin

(b) (4)

<sup>b</sup> 200 mg strength is filled into a size 1 white opaque/pink opaque hard gelatin capsule shell. 250 mg strength is filled into a size 0 pink opaque/pink opaque hard gelatin capsule shell.

(b) (4)



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/s/  
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ZEDONG DONG  
06/01/2011

SARAH P MIKSINSKI  
06/02/2011

**Initial Quality Assessment  
Branch 2  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment**

OND Division: Division of Drug Oncology Products  
NDA: 202-570 (SD-4 or Sq-2 for CMC info.)  
Applicant: Pfizer Inc.  
10646 Science Center Drive  
San Diego, CA 92121

Authorizing US Agent: N/A

Letter Date: 30 March, 2011  
Stamp Date: 30 March, 2011  
PDUFA Goal Date: 30 September, 2011 (priority)  
Trade name: Xalkori (proposed)  
Established Name: Crizotinib  
Dosage Form/Strength: Capsule (200\_mg and 250\_mg)  
Route of Administration: Oral  
Indication: ALK-positive advanced Non-small cell lung cancer (NSCLC).

Regulatory Filing Related IND/NDA/DMF (Form 356h) For 505 (b) (1) IND 073544, DMF  (b) (4)

Assessed by: Haripada Sarker

Yes No

**ONDQA Fileability:** x

**Comments for 74-Day Letter:** x

## Background Summary

This NDA introduces Crizotinib capsules for oral administration containing 200 mg and 250 mg of drug substance. Crizotinib, the drug substance, is a new molecular entity. A 150-mg strength was also developed, but will not be commercialized. This strength was used during development studies and for registration stability. The NDA is a rolling submission, and all sections have been received.

Pfizer adopted a Quality by Design (QbD) approach to develop Crizotinib in accordance with ICH Q8, Q9 and Q10 using risk management approaches, prior knowledge and experimentation. The QbD approach includes DS and DP Manufacturing Process Development and Validation of Analytical Procedures. Applicant referred to various ICH forums to justify the proposed QbD approach utilized for this submission. This information is presented in an expanded section of the respective DS and DP CMC information. The following are some of the key interactions related to CMC.

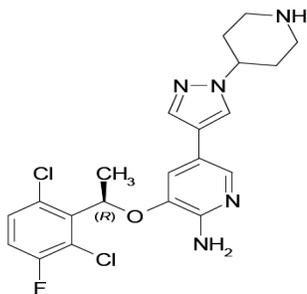
- October 29, 2010. Type-B, CMC specific meeting. Wide range of CMC issues are discussed, including DS starting material, QbD for analytical methods, DP stability plan, and genotoxic impurities.
- February 8, 2011. Pfizer follow-up communication regarding QbD approach in dissolution of DP.

This NDA includes DS and DP quality information in eCTDQ format. The quality information is located in SD-4 in DARRTS (or the Sequence number 2 of the eCTD Global Submit).

## Drug Substance (DS)

The drug substance, Crizotinib, is a white to pale yellow powder, and exhibits pH dependent aqueous solubility. The high solubility of crizotinib drug substance results in a (b) (4) effect that significantly increases the media pH. The DS is defined as class IV (low solubility and low permeability) under the Biopharmaceutics Classification System (BCS). The (b) (4) form utilized as the DS.

Crizotinib has one asymmetric center, resulting in two possible stereoisomers (R and S). The absolute configuration at the 1-position is the R optical isomer. The chemical structure of Crizotinib is below:



Crizotinib manufacturing process (b) (4)

(b) (4)

Crizotinib DS Manufacture, Analytical Testing and Release are performed at:  
Pfizer Ireland Pharmaceuticals  
Little Island  
County Cork  
Ireland

Control of DS is provided

(b) (4)

A QbD approach was utilized to develop and optimize the manufacturing process and HPLC analytical method validation for Crizotinib DS.

*QbD in DS manufacturing process*

(b) (4)

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### Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	Expiration dating will be determined during the review
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √ √ √		Microbiology Pharm/Tox Biopharm Statistics (QbD) OCP/CDRH/CBER LNC DMEPA/ODS <b>EER</b> <b>EA</b>

### Comments and Recommendations

The application is fileable and no 74-Day Letter issues have been identified at this point. Facilities have been entered into EES for inspection. A team approach, including more than one CMC

reviewer, is recommended for this NDA, since this application is an expedited priority (based on medical need) QbD submission.

Haripada Sarker  
CMC Lead

May 2, 2011  
Date

Sarah Pope Miksinski, Ph.D.  
Branch Chief

May 2, 2011  
Date

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HARIPADA SARKER  
05/19/2011

DEBASIS GHOSH  
05/19/2011

SARAH P MIKSINSKI  
05/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## CMC MICROBIOLOGY AND STERILITY ASSURANCE REVIEW REQUEST

TO (Division/Office): **New Drug Microbiology Staff**

**Email to: CDER OPS IO MICRO**

**Mail to: WO Bldg 51, Room 4193**

FROM: Don Henry

PROJECT MANAGER (if other than sender):

REQUEST DATE  
5/6/2011

IND NO.

NDA NO.  
202570

TYPE OF DOCUMENT  
Original NDA submission

DATE OF DOCUMENT  
3/30/2011

NAMES OF DRUG  
**crizotinib**

PRIORITY CONSIDERATION  
priority

PDUFA DATE  
September 30, 2011

DESIRED COMPLETION DATE  
June 30, 2011

NAME OF APPLICANT OR SPONSOR: **Pfizer**

### GENERAL PROVISIONS IN APPLICATION

- |   |   |
|---|---|
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED        | <input type="checkbox"/> CBE-0 SUPPLEMENT                     |
| <input type="checkbox"/> NDA FILING REVIEW NEEDED BY: _____ | <input type="checkbox"/> CBE-30 SUPPLEMENT                    |
| <input type="checkbox"/> BUNDLED                            | <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY |
| <input checked="" type="checkbox"/> DOCUMENT IN EDR         |   |

### COMMENTS / SPECIAL INSTRUCTIONS:

This is a NME. For this solid oral tablet, the sponsor has provided justification for not including the microbial limits testing as part of the specification.

SIGNATURE OF REQUESTER

**Don L. Henry**

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS  EDR  E-MAIL  MAIL  HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR  E-MAIL  MAIL  HAND

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DON L HENRY  
05/06/2011