CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202324Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 202-324, INLYTA (axitinib) Tablets 1mg and 5 mg
Date: 25-JAN-2012

Introduction

INLYTA (axitinib) immediate release tablets (1 mg and 5 mg) are indicated for the treatment of advanced renal cell carcinoma. Dosing is twice daily with or without food. The maximum daily dose is 20 mg as, 10 mg twice daily

This was a QbD application with a team CMC review process within ONDQA (drug substance, drug product, QbD, Biopharm, Analytical MODR, etc.) with consults for the QbD portions including Statictics. There were numerous late-cycle discussions with the applicant (see admin. section below).

There is one CMC related PMC for this application (in DARRTS). It provides for the applicant to validate testing for (b) (4) within 90 (ninety) days.
This is to be included in the action letter.

This is a test the applicant ultimately agreed to adopt late in the review cycle and for which they did not have a validated method. Because this is a well known test with a long and well characterized history, ONDQA is comfortable allowing this time to for validation which should be straightforward.

All other CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies from the CMC standpoint.

ONDQA recommends approval of this NDA.

Administrative

The original submission of this 505(b)(1) NDA was received 13-APR-2011 from Pfizer, Inc. The PDUFA date is 14-FEB-2012. Seven (7) CMC amendments were also reviewed during the review cycle, all of which were received in the last half of the review cycle; two of these within the past week. Most of the amendments were responses to earlier deficiency comments which required multiple cycles to resolve. In this regard, IR letters were sent, 26-SEP-2011, 02-DEC-2011, and 19-JAN-2012. Corresponding teleconferences on 05-DEC-2011, 20-DEC-2011, and 19-JAN-2012 were held with Pfizer to clarify deficiencies and discuss Pfizer's counter-proposals and responses.

Consults: EES acceptable on 04-DEC-2011, Biometrics complete 12-DEC-2011, PharmTox Satisfactory on 06-JAN-2012, Microbiology Satisfactory on 09-JAN-2012, DMEPA satisfactory on 19-JAN-2012.

ONDQA Biopharm portion of the review completed today 25-JAN-2012 as an addendum to a previous approval recommendation.

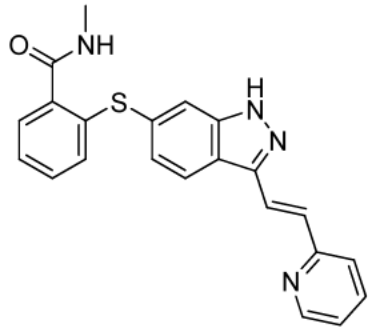
There is one CMC related PMC for this application. It provides for the applicant to validate testing for [redacted] (b) (4) within 90 (ninety) days.

The NDA is supported by nine (9) drug master files (DMFs). All DMFs were assessed for adequacy in the respective chemistry reviews.

ONDQA recommends approval of this NDA.

Drug Substance (axitinib) (a neutral drug substance; NOT a salt or ester)

Chemical Names:
IUPAC: N-Methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide
CAS: Benzamide,N-methyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]-
Molecular Weight: 386.47 g/mol
Molecular Formula: $C_{22}H_{18}N_4OS$
Structure:



The drug substance commercial process consists of [redacted] (b) (4)

The sponsor has adopted a Quality by Design (QbD) based approach for drug substance development based on the principals of ICHQ8 and Q9 including multivariate experimental designs.

The final drug substance axitinib is controlled by the acceptance criteria of quality attributes including identification, assay, impurities, and particle size and crystal form, to ensure the identity, strength, purity, and quality. Stability study with axitinib indicates that it is photo labile. [redacted] (b) (4)

ONDQA recommends approval of this NDA.

Drug Product INLYTA (axitinib) immediate release tablets (1 mg and 5 mg)

The drug product is an immediate release film coated tablet at two different strengths. The 1 mg tablet is red, oval, film coated, tablet de-bossed with "Pfizer" on one side and "1 XNB" on the other. The 5 mg tablet is red, triangular, film coated tablet de-bossed with "Pfizer" on one side and "5 XNB" on the other.

The inactive components of tablets are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry II red 32K15441 which consist of HPMC 2910, titanium dioxide, lactose monohydrate, glycerol triacetate and red iron oxide. All excipients are of compendial grade.

The manufacturing process for the drug product involves (b) (4) The drug product is proposed to be marketed in 180 and 60 count HDPE bottles for the 1 and 5 mg strengths respectively.

The applicant a submitted design space for the manufacturing process and for chromatographic analytical methods for the drug substance and the drug product. The applicant also requested corresponding flexibility for the analytical Method Operable Design Region (MODR) for these methods.

The drug product is proposed to be marketed in 180 and 60 count HDPE bottles for both the 1mg and 5 mg strengths. Based on the stability data provided, the Agency grants a 36 month expiry for both strengths packaged in these container closure systems.

ONDQA recommends approval of this NDA

Place the following language in the action letter:

Based on the provided stability data, an expiration dating period of 36 months is granted for the drug product when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Thank you,

Richard (Rik) Lostritto, Director, Division-I, ONDQA

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

/s/

RICHARD T LOSTRITTO
01/25/2012

NDA 202-324

INLYTA (axitinib) tablets
1 and 5 mg
Pfizer, Inc.
Drug Product Review

Amit K. Mitra, Ph.D
Branch II/ONDQA

for
Division of Drug Oncology Products (Div 1)

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-324

2. REVIEW #:2

3. REVIEW DATE: 22-JAN-2012

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	13-APR-2011
Amendment	21-OCT-2011
Amendment	28-OCT-2011
Amendment	01-NOV-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	21-DEC-2011
Amendment	05-JAN-2012
Amendment	18-JAN-2012
Amendment	20-JAN-2012

7. NAME & ADDRESS OF APPLICANT

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

Representative: Alison Russell, Ph.D

Telephone: (858)-344-4473

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Inlyta
b) Non-Proprietary Name (USAN): Axitinib
c) Code Name/# (ONDC only): AG-013736
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Advanced Renal Cell Carcinoma

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1 and 5 mg

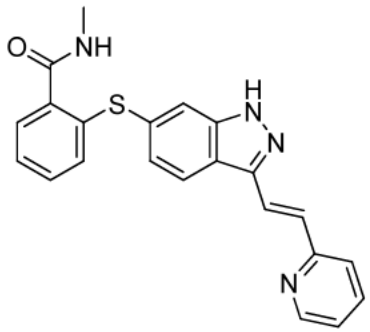
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

_x____Not a SPOTS product

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



N-Methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide

$C_{22}H_{18}N_4OS$. 386.47.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	1	Adequate, Dr. A. K. Mitra	11/30/2011	
	III			4			
	III			4			
	III			3	Adequate, by Dr. C. Strassinger	07/07/2010	
	III			4			

(b) (4)	III	(b) (4)	3	Adequate, by Dr. G. Lunn	6/15/2010	
	III		7			The applicant is not proposing to use this package for commercialization
	III		4			
	III		4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

REVIEWS			
Biometrics			
EES	Acceptable	04-DEC-2011	Mr. M. Stock
Pharm/Tox	N/A		
Biopharm	Satisfactory. However, the reviewer is in the process of writing a second review. The final review will be in the Darrts by Friday, 1/27/2012.	12-DEC-2012	Dr. K. Riviere
LNC			
Methods Validation	Not requested since the application pre-dates the IQP for methods validation		
OPDRA			
EA	Satisfactory	09-DEC-2011	Dr. A. K. Mitra
Microbiology	Satisfactory	09-JAN-2012	Dr. D. A. Miller

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-324

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval with respect to CMC.

Include the following language in the action letter:
Based on the provided stability data, an expiration dating period of 36 months is granted for the drug product when stored at 20-25°C (68-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

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

None

II. Summary of Chemistry Assessments

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

The proposed commercial axitinib drug product is an immediate release film coated tablet at two different strengths. The 1 mg tablet is red, oval, film coated, tablet de-bossed with "Pfizer" on one side and "1 XNB" on the other. The 5 mg tablet is red, triangular, film coated tablet de-bossed with "Pfizer" on one side and "5 XNB" on the other. The inactive components of tablets are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry II red 32K15441 which consist of HPMC 2910, titanium dioxide, lactose monohydrate, glycerol triacetate and red iron oxide. All excipients are of compendial grade. An Information Request was sent to the applicant on the functional attributes of the excipients and their impact of drug product performance. The applicant's response is satisfactory according to the current regulatory standard. The manufacturing process for the drug product involves (b) (4) The drug product is proposed to be marketed in 180 and 60 count HDPE bottles for the 1 and 5 mg strengths respectively.

Axitinib has been formulated in several orally administered dosage forms (b) (4) and an intravenous (IV) solution during different phases of clinical development. The tablets used in early clinical trials were manufactured (b) (4) The proposed

commercial formulation is manufactured (b) (4) The drug product was developed using some elements of Quality by Design elements such as design of experiments, thermodynamic modeling and risk assessment. However, a complete linkage of raw material attributes and process parameters to product quality was not achieved. For example dissolution rate was not monitored during design space evaluation. The proposed commercial manufacturing process is different from the clinical supplies and the registration stability batches (b) (4) The proposed commercial batch size is proposed to be lower than that of the primary registration batches. Several Information Requests were sent to the applicant via several Information Request letters by the ONDQA project manager. The final response provided by the applicant (21-DEC-2011) is satisfactory to the reviewer.

For the Drug Substance summary and review see the review by Dr. J. Tang, Dated 20-JAN-2012.

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

The drug product is proposed to be marketed in 180 and 60 counts HDPE bottles in 1 and 5 mg strengths respectively. The recommended starting oral dose of INLYTA is 5 mg twice daily. INLYTA may be taken with or without food. The maximum daily dose is recommended to be 10 mg twice daily.

The applicant has provided sufficient stability data for a 36 months tentative shelf life under long term storage conditions.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has responded to the latest Information Request letter satisfactorily. Therefore, the application may be approved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

AMIT K MITRA
01/24/2012

SARAH P MIKSINSKI
01/24/2012

NDA 202324

Inlyta™
(Axitinib) Tablets
1 mg and 5 mg

Pfizer, Inc.

Z. Jean Tang, Ph.D
Division of New Drug Quality Assessment I
Branch III

CMC REVIEW OF NDA 202324 DRUG SUBSTANCE
For the Division of Drug Oncology Products (HFD-150)

Table of Contents

CMC Review Data Sheet

1. NDA 202-324

2. REVIEW #: 2

3. REVIEW DATE: 20-Jan-2012

4. REVIEWER: Z. Jean Tang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 63662 Submission	13-NOV-2001
Original IND CMC review by	William C Timme01-AUG-2008
CMC only pre-NDA meeting	

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

Submission(s) Reviewed	Serial Number	DARRTS SD Number	Document Date	Stamp Date
Amendment	0023	024	21-Dec-2011	22-Dec-2011
Amendment	0027	028	20-Jan-2012	20-Jan-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer Inc

Address: 10646 Science Center Drive
San Diego, CA 92121

Representative: Alison Russell, Worldwide Regulatory Strategy

Telephone: (858)622-3234

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: INLYTE™
   b) Non-Proprietary Name: Axitinib
   c) Code Name/# (ONDQA only): NA
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 1 New Molecular Entity
      - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-cancer

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 1 mg and 5 mg

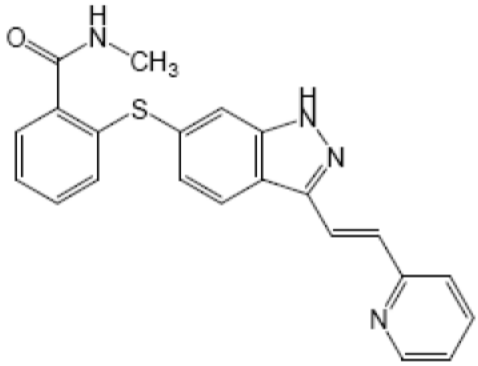
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    __X___Not a SPOTS product

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



Chemical Name:

IUPAC: *N*-Methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide
CAS: Benzamide, *N*-methyl-2-[[3-[(1*E*)-2-(2-pyridinyl)ethenyl]-1*H*-indazol-6-yl]thio]-
JAN: *N*-Methyl-2-({3-[(1*E*)-2-(pyridin-2-yl)ethen-1-yl]-1*H*-indazol-6-yl}sulfanyl)benzamide

Molecular Formula: $C_{22}H_{18}N_4OS$

Molecular Weight: 386.47 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
No DMF for drug substance.

B. Other Documents:
N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistic	Not Recommended for Design Space for (b) (4)	12-DEC-2011	Meiyu Shen
EES	Satisfactory	04-DEC-2011	Shawn Gould & Michele Perry Williams
Drug Substance	Satisfactory	23-JAN-2012	Jean (Zhe) Tang
Drug Product	Satisfactory	23-JAN-2011	Amit Mitra
Analytical	Satisfactory	12-DEC-2011	Donghao (Robert) Liu
Pharm/Tox	Satisfactory	06-JAN-2012	M A Goheer
Biopharm	Satisfactory	12-DEC-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*	• Initial Review • Final Review: Satisfactory	• 08-NOV-2011 • 19-JAN-2012	Denise V. Baugh
EA	Satisfactory	09-DEC-2011	Amit Mitra
Microbiology	Satisfactory	12-JAN-2012	Denise Miller

The Chemistry Review for NDA 202-324

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for APPROVAL with respect to CMC

Include the following language in the action letter:
Based on the provided stability data, an expiration dating period of 36 months is granted for the drug product when stored at 20-25°C (68-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

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

The method and method validation data used to detect (b) (4) and (b) (4) level in Drug Substance will be provided post-approval.

II. Summary of Chemistry Assessments

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

Axitinib (compound number: AG-013736), a substituted indazole achiral derivative with a trans configuration at the olefinic double bond , is an oral, potent, and selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGF) receptors -1, -2, and -3. Axitinib is a white to light yellow powder, and the solubility of axitinib was higher in low pH media (> 1800 µg/ml at pH 1.1) but decreases rapidly across the pH range (0.2 µg/ml at pH 7.8). (b) (4) Its structure was elucidated by IR, HNMR, CNMR, MS, UV/Vis, optical rotation and X-ray crystallography.

The proposed drug substance commercial process consists of (b) (4) The sponsor has adopted a Quality by Design (QbD) based approach for drug substance development based on the principals of ICHQ8 and Q9.

The final drug substance axitinib is controlled by the acceptance criteria of quality attributes including identification, assay, impurities, and particle size and crystal form, to ensure the identity, strength, purity, and quality. Stability study with axitinib indicates that it is photo labile. (b) (4)

For the Drug Product summary and review see the review by Dr. Amit Mitra, dated 24-JAN-2012.

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

Please refer to Dr. Amit Mitra's Review of Drug Product, dated 24-JAN-2012.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has responded to the latest Information Request letter satisfactorily. Therefore, the application may be approved.

III. Administrative

A. Reviewer's Signature
(See appended electronic signature page)

Z. Jean Tang, Ph.D.
CMC Reviewer
Branch III, 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/

ZHE J TANG
01/24/2012

SARAH P MIKSINSKI
01/24/2012

Axitinib
Tablet
1 mg and 5 mg

Pfizer Inc.

CMC Reviewer
(Analytical sections)

Donghao (Robert) Lu, Ph.D.

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

Overall Recommendation: The development and validation results for the analytical sections involved in this NDA are acceptable.

S.4 Control of Drug Substance (Analytical Methods)

S.4.1 Specification (for reference)

(b) (4)

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/s/

DONGHAO R LU
12/12/2011

SARAH P MIKSINSKI
12/12/2011

NDA 202-324

INLYTA (axitinib) tablets
1 and 5 mg
Pfizer, Inc.
Drug Product Review

Amit K. Mitra, Ph.D
Branch II/ONDQA

for
Division of Drug Oncology Products (Div 1)

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-324

2. REVIEW #:1

3. REVIEW DATE: 09-DEC-2011

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	13-APR-2011
Amendment	21-OCT-2011
Amendment	28-OCT-2011
Amendment	01-NOV-2011

7. NAME & ADDRESS OF APPLICANT:

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

Chemistry Review Data Sheet

Representative: Alison Russell, Ph.D

Telephone: (858)-344-4473

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Inlyta
b) Non-Proprietary Name (USAN): Axitinib
c) Code Name/# (ONDC only): AG-013736
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: 505 (b)(1)

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1 and 5 mg

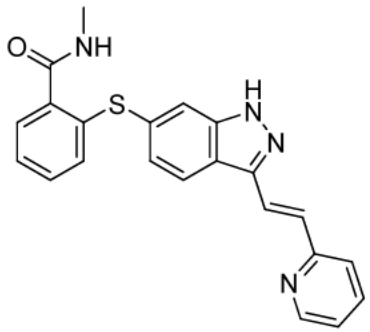
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

_x____Not a SPOTS product

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



N-Methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide

$C_{22}H_{18}N_4OS$. 386.47.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	1	Adequate, Dr. A. K. Mitra		
	III			4			
	III			4			
	III			3	Adequate, by Dr. C. Strassinger	07/07/2010	
	III			4			

(b) (4)	III		(b) (4)	3	Adequate, by Dr. G. Lunn	15-JUN-2010	
	III			7			The applicant is not proposing to use this package for commercialization
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

REVIEWS			
Biometrics			
EES	Acceptable	04-DEC-2011	Mr. M. Stock
Pharm/Tox	N/A		
Biopharm	Pending		
LNC			
Methods Validation			
OPDRA			
EA	Satisfactory	09-DEC-2011	Dr. A. K. Mitra
Microbiology	Pending		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-088

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable pending resolution of several CMC issues provided in the "**Basis for Approvability or Not-Approval Recommendation"** section.

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

II. Summary of Chemistry Assessments

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

The proposed commercial axitinib drug product is an immediate release film coated tablet at two different strengths. The 1 mg tablet is red, oval, film coated, tablet de-bossed with "Pfizer" on one side and "1 XNB" on the other. The 5 mg tablet is red, triangular, film coated tablet de-bossed with "Pfizer" on one side and "5 XNB" on the other. The inactive components of tablets are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry II red 32K15441 which consist of HPMC 2910, titanium dioxide, lactose monohydrate, glycerol triacetate and red iron oxide. All excipients are of compendial grade. An Information Request was sent to the applicant on the functional attributes of the excipients and their impact of drug product performance. The applicant's response is satisfactory according to the current regulatory standard. The manufacturing process for the drug product involves (b) (4) The drug product is proposed to be marketed in 180 and 60 count HDPE bottles.

Axitinib has been formulated in several orally administered dosage forms (b) (4) and an intravenous (IV) solution during different phases of clinical development. The tablets used in early clinical trials were manufactured (b) (4) The proposed commercial formulation is manufactured (b) (4) The drug product was developed using some elements of Quality by Design elements such as design of

experiments, thermodynamic modeling and risk assessment. However, a complete linkage of raw material attributes and process parameters to product quality was not achieved. For example dissolution rate was not monitored during design space evaluation. The proposed commercial manufacturing process is different from the clinical supplies and the registration stability batches (b) (4) The proposed commercial batch size is proposed to be lower than that of the primary registration batches. The applicant's post-approval stability commitment is inadequate. Several Information Requests were sent to the applicant. To date, applicant has not responded to several of those Information Requests satisfactorily.

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

The drug product is proposed to be marketed in 180 and 60 count HDPE bottles in 1 and 5 mg strengths. The recommended starting oral dose of INLYTA is 5 mg twice daily. INLYTA may be taken with or without food. The maximum daily dose is recommended to be 10 mg twice daily.

The applicant has provided sufficient stability data for a 36 months tentative shelf life under long term storage conditions.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has not responded to the latest Information Request letter. Therefore, a complete response is recommended to be sent to the applicant as follows:

1. As previously mentioned, notification of all changes including changes to process parameters are to be provided in accordance with 21CFR 314.70. Therefore the process description (section P.3.3) is to be provided in accordance with 21 CFR 314.50 which indicates that the applicant submits: "*The proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product.*" Therefore, to meet these regulatory requirements, your options are as follows:
    a. Provide a master batch record to any section of module 3, with a reference/link to the master batch record in the process description (section P.3.3)
    b. Provide a process description to section P.3.3 that is comparably detailed to the master batch record.

2. The justification for not including coating weight upper limit is not acceptable. Based on the information provided in the NDA, the dissolution data do not support a film coating specification (b) (4) Adopt an upper limit for coating weight based on the provided dissolution data to resolve this issue.

3. The rationale provided for not performing microbial limits testing is not adequate as there is insufficient manufacturing history on which to evaluate the process control over time and manufacturing environmental conditions.

   Microbial limit specifications should be set for release and stability. Once a satisfactory product history has been established, a post-approval supplement may be submitted to the FDA request the waiver of microbial limits testing during release; however the testing should remain in the stability program.

   Include microbial limits in the drug product specification to resolve this issue.

4. The justification for not conducting assay on stability is not acceptable. Update the post-approval stability protocol to include assay testing to resolve this issue.

5. It is not clear from the stability Table 3.2.P.8.1-1 of amendment, dated 10/28/2011 that the batch size for the primary stability lots are the same as that of the proposed commercial lot. Therefore, your justification for not making a post approval stability commitment is not acceptable. Also, revise the sampling points for both long term and accelerated conditions to meet the requirements of ICH Q1(R2). Revise the post-approval stability commitment and include required sampling points and storage conditions to resolve this issue.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

AMIT K MITRA
12/09/2011

SARAH P MIKSINSKI
12/12/2011

NDA 202324

Inlyta™
(Axitinib) Tablets
1 mg and 5 mg

Pfizer, Inc.

Z. Jean Tang, Ph.D
Division of New Drug Quality Assessment I
Branch III

CMC REVIEW OF NDA 202324 DRUG SUBSTANCE
For the Division of Drug Oncology Products (HFD-150)

Table of Contents

CMC Review Data Sheet

1. NDA 202-324

2. REVIEW #: 1

3. REVIEW DATE: 02-Sep-2011

4. REVIEWER: Z. Jean Tang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 63662 Submission	13-NOV-2001
Original IND CMC review by	William C Timme01-AUG-2008
CMC only pre-NDA meeting	

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

Submission(s) Reviewed	Serial Number	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submissions	0000	001	14-Apr-2011	14-Apr-2011
Amendment	0011	012	21-Oct-2011	21-Oct-2011
Amendment	0013	015	28-Oct-2011	28-Oct-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc
Address:	10646 Science Center Drive San Diego, CA 92121
Representative:	Alison Russell, Worldwide Regulatory Strategy

Telephone: (858)622-3234

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: INLYTE™
   b) Non-Proprietary Name: Axitinib
   c) Code Name/# (ONDQA only): NA
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 1 New Molecular Entity
      - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-cancer

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 1 mg and 5 mg

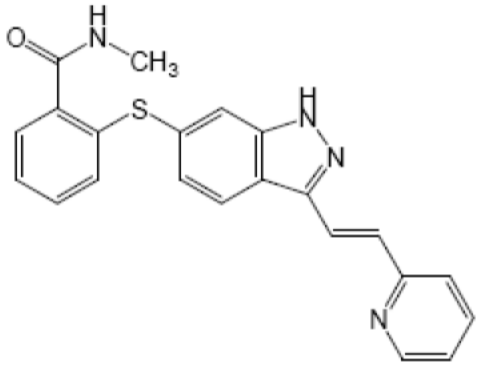
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    __X___Not a SPOTS product

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



Chemical Name:

IUPAC: *N*-Methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide
CAS: Benzamide, *N*-methyl-2-[[3-[(1*E*)-2-(2-pyridinyl)ethenyl]-1*H*-indazol-6-yl]thio]-
JAN: *N*-Methyl-2-({3-[(1*E*)-2-(pyridin-2-yl)ethen-1-yl]-1*H*-indazol-6-yl}sulfanyl)benzamide

Molecular Formula: $C_{22}H_{18}N_4OS$

Molecular Weight: 386.47 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
No DMF for drug substance.

B. Other Documents:
N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistic	Not Recommended for Design Space for (b) (4)	12-DEC-2011	Meiyu Shen
EES	Approval	04-DEC-2011	Shawn Gould & Michele Perry Williams
Drug Substance	Complete Response	12-DEC-2011	Jean (Zhe) Tang
Drug Product	Complete response	12-DEC-2011	Amit Mitra
Analytical	Satisfactory	12-DEC-2011	Donghao (Robert) Liu
Pharm/Tox	Pending	12-DEC-2011	
Biopharm	Satisfactory	09-DEC-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*	• Initial Review • Final Review Pending	• 08-NOV-2011 • 12-DEC-2011	Denise V. Baugh
EA	Satisfactory	09-DEC-2011	Amit Mitra
Microbiology	Pending	12-DEC-2011	Denise Miller

The Chemistry Review for NDA 202-324

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is not recommended for APPROVAL from a CMC perspective due to the unsolved deficiencies on the page 114.

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

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE

Axitinib (compound number: AG-013736), a substituted indazole achiral derivative with a trans configuration at the olefinic double bond , is an oral, potent, and selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGF) receptors -1, -2, and -3. Axitinib is a white to light yellow powder, and the solubility of axitinib was higher in low pH media (> 1800 µg/ml at pH 1.1) but decreases rapidly across the pH range (0.2 µg/ml at pH 7.8). (b) (4) [redacted] Its structure was elucidated by IR, HNMR, CNMR, MS, UV/Vis, optical rotation and X-ray crystallography.

The proposed drug substance commercial process consists of (b) (4) [redacted] The sponsor has adopted a Quality by Design (QbD) based approach for drug substance development based on the principals of ICHQ8 and Q9.

The final drug substance axitinib is controlled by the acceptance criteria of quality attributes including identification, assay, impurities, and particle size anf crystal form, to ensure the identity, strength, purity, and quality. Stability study with axitinib indicates that it is photo labile. An (b) (4) [redacted] has been granted based on the stability data presented in the NDA dossier.

DRUG PRODUCT

Please refer to Dr. Amit Mitra's Review of Drug Product

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

Please refer to Dr. Amit Mitra's Review of Drug Product.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (202-324) is not recommended for APPROVAL from a CMC perspective due to the unsolved deficiencies on the page 114.

III. Administrative

A. Reviewer's Signature
(See appended electronic signature page)

Z. Jean Tang, Ph.D.
CMC Reviewer
Branch III, Division I, ONDQA
CDER, FDA

B. Endorsement Block
(See appended electronic signature page)

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

C. CC Block entered electronically in DARRTS

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/s/

ZHE J TANG
12/12/2011

SARAH P MIKSINSKI
12/12/2011

To: NDA 202324, INLYTA® (axitinib) tablets, drug product manufacturing
From: Amit K. Mitra, Ph.D
Through: Sarah Pope Miksinski, Ph.D
Subject: Chemistry Manufacturing & Controls Considerations for Drug Product Manufacturing and Quality

The purpose of this memo is to outline the manufacturing process for 1 and 5 mg film coated axitinib tablets and to discuss the control strategy proposed in the NDA 202324. This memo is not intended to be used as inspectional instructions.

Axitinib is a BCS class II drug and photo-unstable. It is indicated for advanced renal cell carcinoma.

The NDA was submitted by Pfizer, Inc. The drug product is proposed to be manufactured and released by Pfizer manufacturing Deutschland, Germany. The 1 mg axitinib film coated tablets are red, film coated, oval shaped tablets debossed with "Pfizer" on one side and "1 XNB" on the other. The 5 mg axitinib film coated tablets are red triangular shaped tablets debossed with "Pfizer" on one side and "5 XNB" on the other. The drug product is packaged in high density polyethylene (HDPE) bottles containing desiccant with induction seal and child-resistant closures (b) (4)

The drug product is manufactured (b) (4) Also, raw material properties could be critical to content uniformity.

The (b) (4) tablet is film coated with HPMC 2910 (Hypromellose 15 cP) using titanium dioxide (b) (4), red iron oxide (b) (4), lactose monohydrate, and (b) (4) triacetin (b) (4). Since the 5 mg tablet is triangular shape the coating uniformity of the tablet (b) (4) could be critical to the success of the coating process. See Attachment 1 for component/composition.

The proposed commercial axitinib tablets are manufactured (b) (4) Process optimization and design space establishment were achieved through iterations of risk assessment, multivariate and univariate studies with small scale development trials,

modeling tools and knowledge gained from larger scale trials at the proposed commercial manufacturing site. The process flow diagram is provided in Attachment 2.

The [redacted] (b) (4) used in the manufacture of the proposed commercial axitinib tablet is claimed by the applicant to be the same as that used in development. The reviewer would appreciate input from the inspectors based on observations during the inspection process to verify this claim. The applicant's control strategy is based on prior knowledge and design of experiments in development scale (See Attachment 3). The applicability of the design space developed in small scale to the proposed commercial scale is to be determined.

The applicant has not provided a Master Batch Record for the drug product. The applicant indicated the following in the introduction section of the executed batch record: "The executed manufacturing batch records for the following representative batches of axitinib 1 mg and 5 mg tablets manufactured at the commercial manufacturing site, Pfizer Manufacturing Deutschland GmbH (Freiberg, Germany) are provided in this document". The executed batch records for [redacted] (b) (4) 1 and 5 mg tablets were provided. However, the proposed commercial 1 mg tablet is oval in shape. The applicant indicated that 1 mg oval tablet representative batch record is available upon request and it will be requested by the reviewer via an Information Request.

The drug product is controlled by conventional specification [redacted] (b) (4) and microbial limits are not part of the specification (see Attachment 4).

Reviewer's risk assessment at various stages of manufacturing process:

1) It is not clear how the [redacted] (b) (4) uniformity would be maintained post approval and the design space would be verified for changes in raw material properties. It is not clear from the application whether the applicant is conducting any functionality test such as particle size, bulk density etc. [redacted] (b) (4)

2) Since no Master Batch Record (MBR) was provided, the reviewer would appreciate examination of the MBR to determine if it is representative of those in the design space (see Attachments 3 and 4) and in previous batches. The applicant indicated in Table 3.2.R-2 under executed batch records that the executed batch record for two lots of 1 mg oval tablets (lot 965638-3000108, manufactured on October 2008 and lot 965608-3000, manufactured on April 2010) will be made available upon request. Those two batch records are actually representative commercial lots. Therefore, the reviewer would appreciate an inspectional review for all quality defects including broken tablets, uneven coating, chipping etc.

3) [redacted] uniformity test result was not part of the submitted executed batch record. This is a relatively high risk since the drug content is low. The reviewer would appreciate if [redacted] uniformity data of the registration and clinical batches be examined for appropriate sampling technique and results.

   Furthermore, the applicant is using NIR for determination of [redacted] uniformity (written as: "for information only" in the executed batch record). The reviewer would appreciate determination during inspection of whether the [redacted] uniformity determination by NIR is included in the MBR, and if the quality of NIR data [redacted] assures uniformity, especially for the 1 mg tablet formula.

4) The applicant's control strategy for drug product quality consists of a combination of conventional specification, control of key and critical attributes/parameters, and control of non-critical attributes/parameters (See Attachment 4).

   The sponsor proposed a design space to support flexibility in operating conditions for the drug product. The quality systems should be appropriate for handling movements within and outside the design space. Movements into previously unverified areas of the design space should trigger a more detailed evaluation of potential risks to product quality. The quality systems should also be appropriate for handling updates and changes to the design space and associated control strategy.

For questions regarding drug product Chemistry Manufacturing and Controls please contact Amit K. Mitra, Ph.D, Phone: 301-796-1420, E-mail: amit.mitra@fda.hhs.gov.

Attachment 1
Component/Composition (1 mg Tablet)

Component	Function	Reference to Standard	Theoretical Unit and/or Formula (mg)
Axitinib	Active	Pfizer	1.000[1]
Microcrystalline Cellulose[2]	(b) (4)	NF, Ph. Eur.,JP	(b) (4)
Lactose Monohydrate		NF, Ph. Eur.,JP	
Croscarmellose Sodium		NF, Ph. Eur.,JP	
Magnesium Stearate		NF, Ph. Eur.,JP	
(b) (4)			
Film Coat			
Opadry® II Red 32K15441		Pfizer[3]	
(b) (4)		USP, Ph. Eur., JP	
Total Finished Tablet			

Note: NF=National Formulary; USP=the United States Pharmacopeia; Ph.Eur.=the European Pharmacopeia; JP=Japanese Pharmacopeia

(b) (4)

Opadry® II Red (32K15441) contains:

Name of Ingredients	Reference to Standard	Unit Formula (mg/tablet)
HPMC 2910/Hypromellose 15cP	USP, Ph. Eur, JP	(b) (4)
Titanium dioxide	USP, FCC, Ph. Eur, JP	
Lactose Monohydrate	NF, Ph. Eur, JP	
Triacetin (Glycerol Triacetate)	USP, FCC, JPE, (Ph. Eur)	
Red Iron Oxide	NF, JPE	

Component/composition (5 mg tablet)

Component	Function	Reference to Standard	Theoretical Unit and/or Formula (mg)
Axitinib	Active	Pfizer	5.000[1]
Microcrystalline Cellulose[2]	(b) (4)	NF, Ph. Eur.,JP	(b) (4)
Lactose Monohydrate		NF, Ph. Eur.,JP	
Croscarmellose Sodium		NF, Ph. Eur.,JP	
Magnesium Stearate		NF, Ph. Eur.,JP	
(b) (4)			
Film Coat			
Opadry® II Red 32K15441		Pfizer[3]	
(b) (4)		USP, Ph. Eur., JP	
Total Finished Tablet			

Note: NF=National Formulary; USP=the United States Pharmacopeia; Ph.Eur.=the European Pharmacopeia; JP=Japanese Pharmacopeia

(b) (4)

Opadry® II Red (32K15441) contains:

Name of Ingredients	Reference to Standard	Unit Formula (mg/tablet)
HPMC 2910/Hypromellose 15cP	USP, Ph. Eur, JP	(b) (4)
Titanium dioxide	USP, FCC, Ph. Eur, JP	
Lactose Monohydrate	NF, Ph. Eur, JP	
Triacetin (Glycerol Triacetate)	USP, FCC, JPE, (Ph. Eur)	
Red Iron Oxide	NF, JPE	

Reviewer's comment: The selection of the component/composition is mostly based on prior knowledge. The excipients are suitable for the intended process.

Attachment 2

The proposed commercial batch size was reported as (b) (4). The executed batch record suggests a batch size of approximately (b) (4) The manufacturing process as provided in section **3.2.P.3.3** is given below:

FLOW DIAGRAM OF MANUFACTURING PROCESS:

(b) (4)

The manufacturing process description of the 5 mg tablet is similar; therefore, it is not repeated here.

Attachment 3

Summary of applicant's control strategy

(b) (4)

Applicant's summary of initial process optimization

Critical step during the manufacturing process: The applicant has identified (b) (4)

Manufacturing process steps and equipment for development, clinical, formal registration stability and the proposed commercial batches:

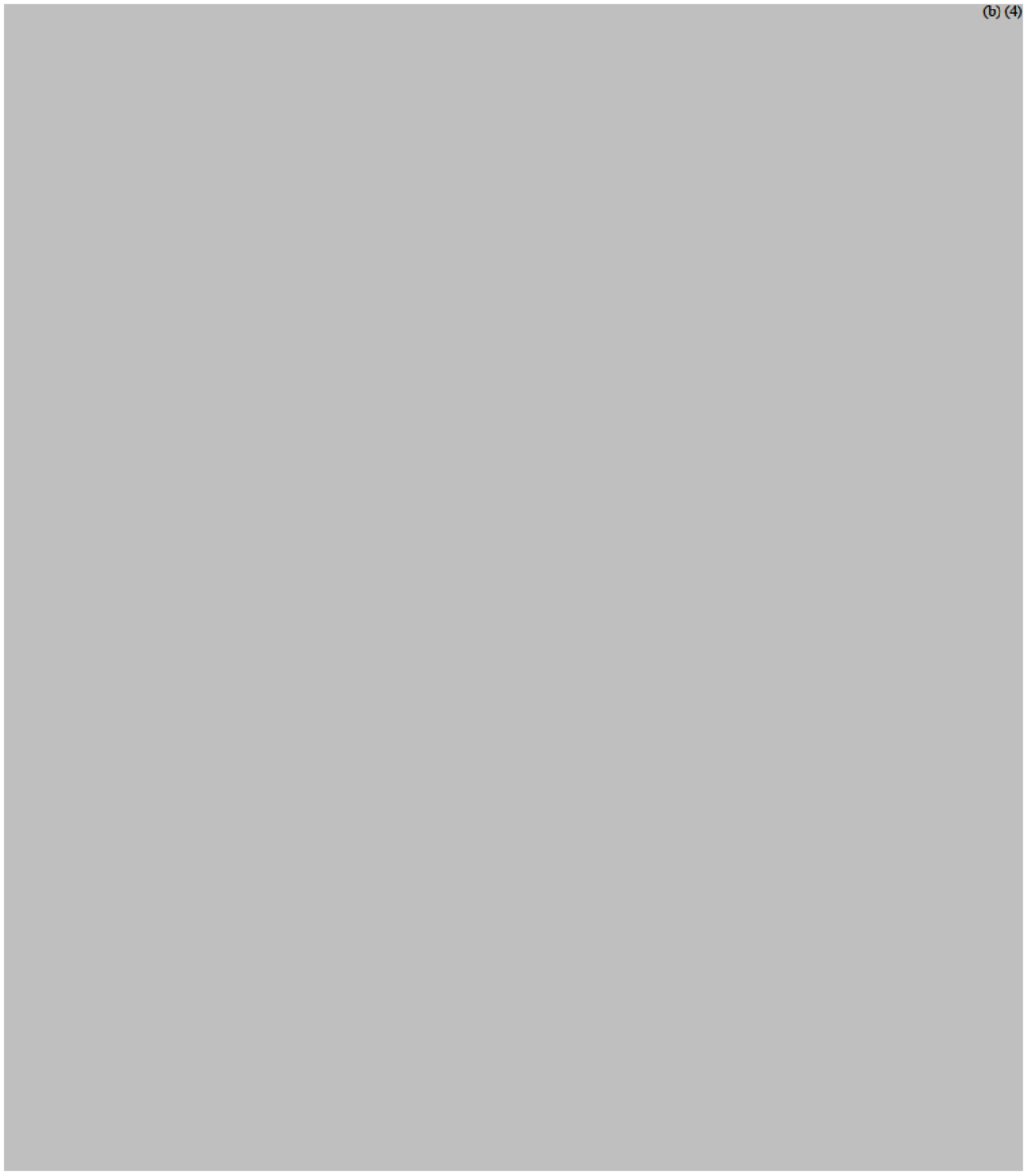
(b) (4)

Attachment 4: Control Strategy

Drug Product specification

Test Name	Specification Acceptance Criteria
Appearance	1 mg Tablet Red oval film coated tablet debossed "*Pfizer*" on one side and "1" and "*XNB*" on the other 5 mg Tablet Red triangular film coated tablet debossed "*Pfizer*" on one side and "5" and "*XNB*" on the other
Identification (HPLC)	(b) (4)
Identification (UV)	
Assay (HPLC)	
Individual Known Degradation Products (Area %) (HPLC)	
Individual Unknown Degradation Products (Area %) (HPLC)	
Total Degradation Products (Area %) (HPLC)	
Uniformity of Dosage Units (HPLC)	
Dissolution (HPLC)	

Key and Critical Attributes/Parameters



Non-Critical Attributes/Parameters

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/s/

AMIT K MITRA
06/13/2011

JANICE T BROWN
06/13/2011
Janice Brown for
Sarah Pope Miksinski, Ph.D

DATE: June 1, 2011
TO: Extended Axitinib (NDA 202-324) Review Team
FROM: Jean Tang, Ph.D. 301-796-4956, zhe.tang@fda.hhs.gov (on behalf of the CMC review team)
THROUGH: Sara Pope-Miksinski, Ph.D.

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

Purpose:
The objective of this memo is to provide: a brief overview of the drug substance Axitinib manufacturing process, a summary of QbD approaches proposed in this application, and the reviewer's suggested considerations for pre-approval inspections regarding the QbD approaches. This memo is not intended to provide inspectional instructions.

Background:
NDA 202-324 was submitted on April 14, 2011 under 505(b)(1) by Pfizer, Inc. for axitinib 1 mg and 5 mg immediate release tablets. The proposed indication is treatment of Advanced Renal Cell Carcinoma (RCC). The application has been granted "Standard" review status.

Drug Substance Summary of Manufacturing:
The (b) (4) route scheme is provided in Appendix I. The proposed drug substance commercial process consists of (b) (4) The sponsor has adopted a Quality by Design (QbD) based approach for drug substance development based on the principals of ICHQ8 and Q9.

QbD Approaches and Control Strategies (Manufacturing):
The sponsor employed a systematic approach to determine the important aspects of the drug substance manufacture and the design space, the primary elements of which includes risk assessment, quality target product profile (QTPP), the identification of the critical quality attributes (CQAs), the process parameters (CPP, KPP) that have a potential impact on these CQAs, and a description of the experiments (DoEs) undertaken to determine the design space ranges for the drug substance manufacturing processes.

The critical quality attributes of axinitib are included in the drug substance specification (Appendix II). The specification is based on the traditional end product release, and there is no real time release testing (RTRT) proposed for any of the testing defined in the specifications.

Appendix III lists the key and critical process parameters for each step, as well as the regulatory commitment for the operating range. Typically, plans for handling movement within the design space are documented within the firm's Quality System.

Reviewer's Preliminary Assessment of Risk (Manufacturing):
The synthesis of Axitinib consists of (b) (4) One of the most important CQAs is the level of the impurity. The assurance

of the implementation of the control strategy and operation within the design space are necessary to meet the specifications of impurities during the manufacture process.

(b) (4)

Consideration for the inspection (Manufacturing)

- This application includes a design space for drug substance manufacturing. The quality systems should be appropriate for handling movements within the design space. Movements to previously unverified areas of the design space should trigger a more detailed evaluation of potential risks to product quality. The quality systems should also be appropriate for handling updates and changes to the design space and associated control strategy.
- The supply chain management and control needs to be evaluated to ensure the consistent quality of the raw materials and starting materials (b) (4)

QbD Approach for Analytical Method Validation
The development of an HPLC method for identity, assay and purity evaluation of axitinib drug substance is based on QbD principles. The process for developing and implementing an analytical method with QbD principles is analogous to that described for pharmaceutical manufacturing in ICH Q8. This process includes a definition of the necessary requirements of the measurement system, determination of a Method Operable Design Region (MODR; akin to a design space) whereby method conditions will meet the established requirements, continuous verification that the method is operating within the requirements through use of a control strategy, and implementation of a process for change management through the product lifecycle based on the rich development knowledge.

The sponsor proposes MODR as well as post-approval change control strategy as described in Appendix IV.

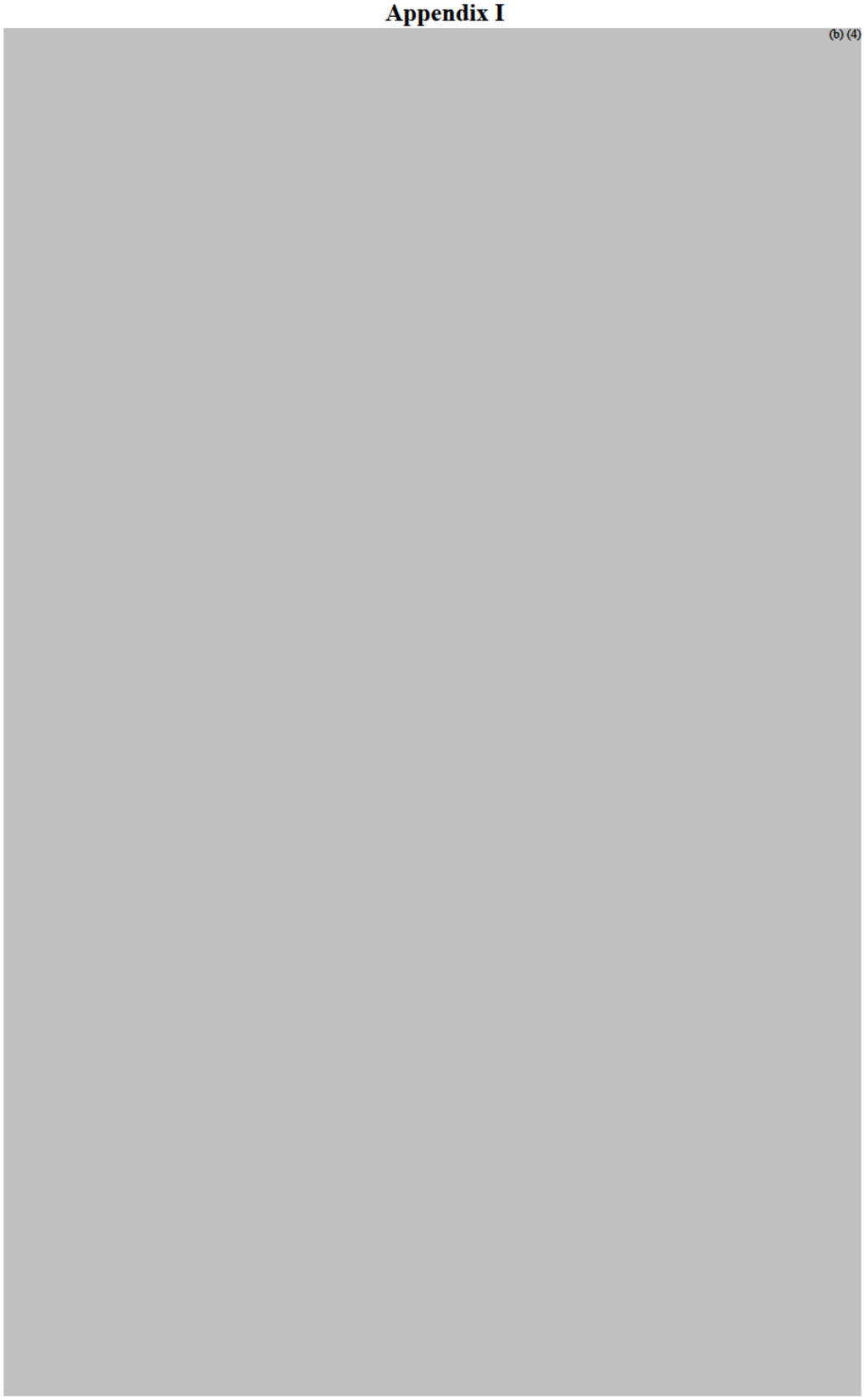
Reviewer's Preliminary Assessment of Risk (Analytical)
Multivariate designed experiments (DoE) were used to determine the method operable design region (MODR), including robustness and ruggedness assessment. The results of the initial robustness experiments were used identify those parameters that impacted chromatographic performance. A statistical model of these results was used to defined the parameter ranges over which the method is expected to meet the system suitability and ATP requirements. These ranges defined a preliminary experimental design space. A subsequent experimental study was constructed using those parameters with the largest collective impact on resolution and Limit of Quantitation (LOQ), as these attributes are critical to meet the ATP. Based on the subsequent experimental study, the final statistical MODR model is constructed to provide the operating ranges for the method. However the flexibility of operating parameters within MODR, the synergetic impact of operating parameters within MODR on the ATP and the potential impact on

the reproducibility of retention time of the analyte when operating method within MODR have not been evaluated.

Consideration for Inspection (Analytical)

There are two elements included in the method control strategy: adherence to the MODR and the chromatographic performance check (e.g. system suitability). Firm's internal procedures should be appropriate to ensure the method operation within MODR and system suitability upon movements within MODR.

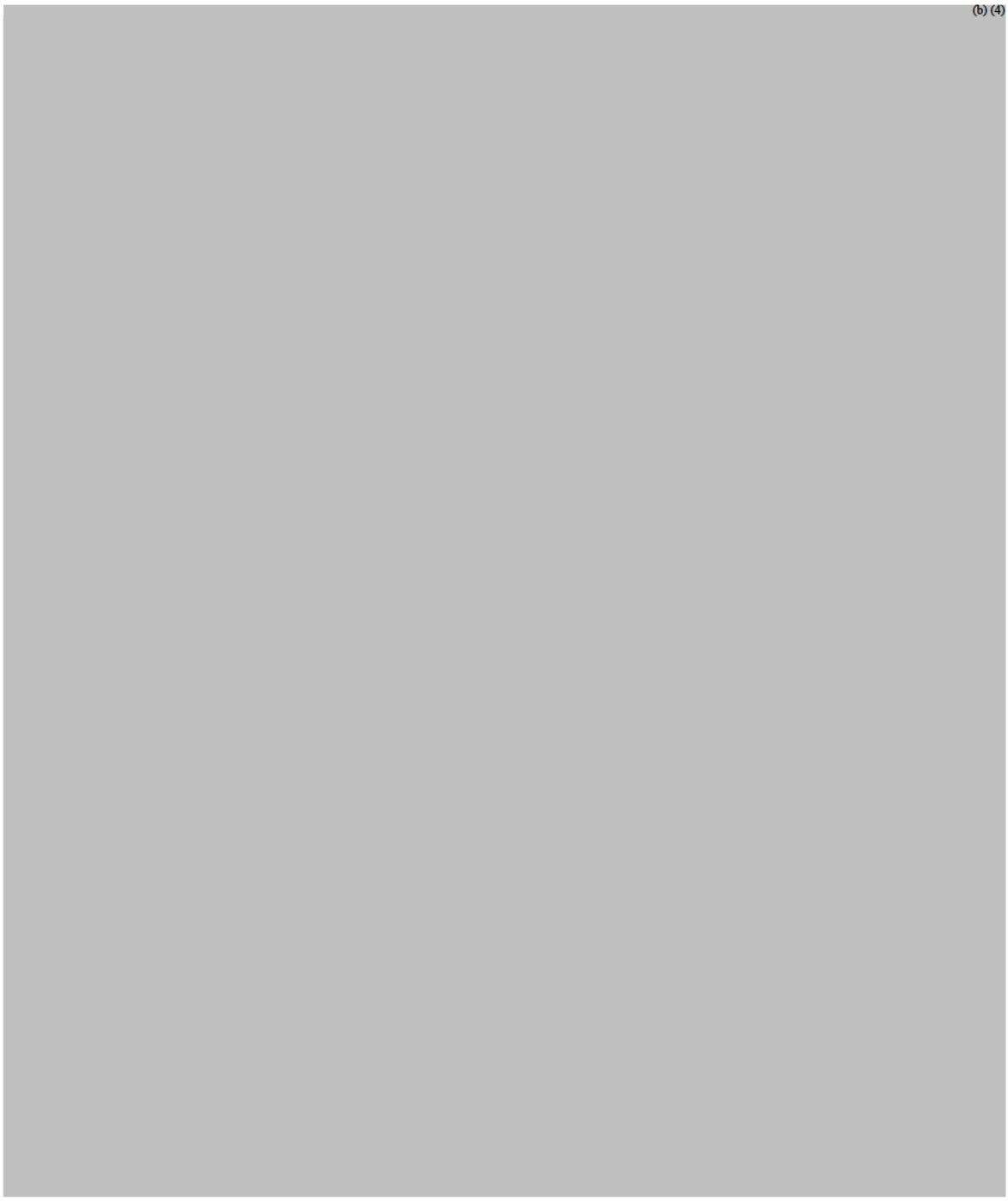
Appendix I



Abbreviations:

Appendix II

(b) (4)



Appendix III

Appendix IV

MODR Acceptable Ranges for Axitinib Drug Substance Assay/Purity Method

Proposed Post-Approval Change Control Strategy

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/s/

ZHE J TANG
06/13/2011

HARIPADA SARKER
06/13/2011
Sign-off on behalf of Sarah Pope Miksinski