CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201292Orig1s000

CHEMISTRY REVIEW(S)

MEMO TO FILE

NDA: 201292

From: Li-Shan Hsieh Ph.D.
CMC Reviewer, Branch II, Division I, ONDQA

To: Ali Al-Hakim Ph.D.
Branch Chief, Division I, ONDQA

Date: June 27, 2013

SUBJECT: EES Acceptable for NDA 201292

The original CMC review for NDA 201292 dated 22-Apr-2013 has recommended Approval for this NDA pending overall recommendation from the Office of Compliance. However, Office of Compliance has issued an overall acceptable recommendation for this application dated June 26, 2013. Therefore, the NDA is recommended for approval from CMC perspective.

The EES report is attached to this Memo.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 201292/000	**Action Goal:**	
Stamp Date:	15-NOV-2012	**District Goal:**	15-MAR-2013
Regulatory:	15-JUL-2013		
Applicant:	BOEHRINGER INGELHEIM	**Brand Name:**	Afatinib
	900 RIDGEBURY RD	**Estab. Name:**	
	RIDGEFIELD, CT 06877	**Generic Name:**	Afatinib
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	107	001; TABLET, FILM COATED; AFATINIB; EQ 20MG BASE 002; TABLET, FILM COATED; AFATINIB; EQ 30MG BASE 003; TABLET, FILM COATED; AFATINIB; EQ 40MG BASE	

(b) (4)

Application Comment:

FDA Contacts:	L. HSIEH	Prod Qual Reviewer		3017961682
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	D. VARNEY	Regulatory Project Mgr	(HFD-107)	3017960297
	L. ZHOU	Team Leader		3017961781

Overall Recommendation:	ACCEPTABLE	on 26-JUN-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 06-FEB-2013	by EES_PROD		
	PENDING	on 07-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: D-U-N-S: 340245275
RESPONSIBILITIES:
TESTING OF TABLETS, INCLUDING STABILITY TESTING (on 07-DEC-2012 by J. MARTIN (HFV-530) 3017962072)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-DEC-2012				MARTINJ
SUBMITTED TO DO NME	10-DEC-2012	Product Specific			SHARPT
DO RECOMMENDATION	18-DEC-2012			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	27-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: 9610492 FEI: 3002806556

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

BINGER STREET 173
INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

Establishment Comment: COMPLETE ADDRESS LISTED AS: BINGER STRASSE173, 55216 INGELHEIM AM, RHEIN GERMANY,
D-U-N-S: 551147440
SITE RESPONSIBILITIES LISTED AS:MANUFACTURING OF BULK TABLETS,
TESTING OF TABLETS, INCLUDING STABILITY TESTING, TEST ON
(b) (4) DEGRADATION, TESTING OF EXCIPIENTS, PRIMARY PACKAGING AND LABELING, SECONDARY PACKAGING AND LABELING MANUFACTURING, PACKAGING, LABELING, AND ANALYTICAL TESTING INCLUDING STABILITY TESTING
CONTACT EMAIL:
WOLFGANG.WERRA@BEOHRINGERINGELHEIM.COM (on 27-NOV-2012 by J. MARTIN (HFV-530) 3017962072)
RESPONSIBILITIES LISTED AS: MANUFACTURING, PACKAGING, LABELING,AND ANALYTICAL TESTING INCLUDING STABILITY TESTING
D-U-N-S: 551147440
(on 27-NOV-2012 by J. MARTIN (HFV-530) 3017962072)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** POTENTIAL OAI

TABLETS, PROMPT RELEASE POTENTIAL OAI

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-DEC-2012				MARTINJ
SUBMITTED TO DO	11-DEC-2012	Product Specific			SHARPT
UNDER REVIEW	12-DEC-2012				PHILPYE
DO RECOMMENDATION	15-APR-2013			WITHHOLD	PHILPYE
				PENDING REGULATORY ACTION WITH	
UNDER REVIEW	05-JUN-2013				PHILPYE
DO RECOMMENDATION	25-JUN-2013			ACCEPTABLE	PHILPYE
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.				BASED ON FILE REVIEW	
OC RECOMMENDATION	26-JUN-2013			ACCEPTABLE	WILLIAMSJU
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	06-DEC-2012				MARTINJ
SUBMITTED TO DO	12-DEC-2012	Product Specific			STOCKM
UNDER REVIEW	18-DEC-2012				PHILPYE
DO RECOMMENDATION	15-APR-2013			WITHHOLD	PHILPYE
				PENDING REGULATORY ACTION WITH	
UNDER REVIEW	05-JUN-2013				PHILPYE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DO RECOMMENDATION	25-JUN-2013	ACCEPTABLE	PHILPYE
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.		BASED ON FILE REVIEW	
OC RECOMMENDATION	26-JUN-2013	ACCEPTABLE	WILLIAMSJU
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.		DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: RESPONSIBILITIES LISTED AS:
TESTING OF TABLETS, INCLUDING STABILITY TESTING, TEST ON (b) (4) DEGRADATION
D-U-N-S: 334456161 (on 27-NOV-2012 by J. MARTIN (HFV-530) 3017962072)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-DEC-2012				MARTINJ
SUBMITTED TO DO	12-DEC-2012	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	18-DEC-2012	Product Specific			PHILPYE
INSPECTION SCHEDULED	19-MAR-2013		30-APR-2013		IRIVERA
DO RECOMMENDATION	13-MAY-2013			ACCEPTABLE	PHILPYE
AS PER M. FARBMAN, ATL				INSPECTION	
OC RECOMMENDATION	13-MAY-2013			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

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/s/

LI SHAN HSIEH
06/27/2013

ALI H AL HAKIM
06/27/2013

ONDQA Division Director's Memo
NDA 201292, Gilotrif® (Afatinib) Tablets
20mg, 30 mg, 40 mg, (b) (4) tablets

Date: 27 June, 2013

Introduction

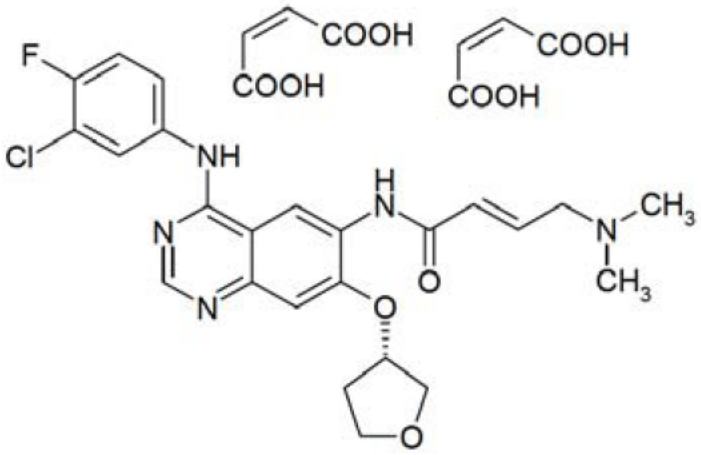
Afatinib (free base) is a new molecular entity chemically synthesized small molecule; the salt form is Afatinib dimaleate (see structure below). CMC review #1 dated April 22, 2013, indicated that Office of Compliance recommendation for the application was pending. However, CMC memo dated June 27, 2013 reported that Office of Compliance has updated their recommendation to acceptable. Therefore, all CMC-related reviews/issues were completed and found acceptable for this NDA including acceptable recommendation from office of compliance.

ONDQA recommends an Approval action for the NDA

Summary

Chemical Name: 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-(2E)-, (2Z)-2-butenedioate (1:2)

Chemical Structure



Molecular Formula: $C_{24}H_{25}ClFN_5O_3 \cdot 2\ C_4H_4O_4$
Molecular Wright: 718.1 g/mol (salt form), 485.9 g/mol (free base)

Afatinib (free base) is a new molecular entity chemically synthesized small molecule; the salt form is Afatinib dimaleate. (b) (4)

[redacted]. The synthetic process has been optimized during drug development to improve the robustness of the process, the quality of intermediates and the drug substance. Potential impurities and degradants were identified and controlled as appropriately.
The release specification and analytical procedures are described in sufficient detail and validated for their intended uses. Acceptance criteria were justified by batch analysis data and during clinical studies. Reference standards have been established for drug substance and potential impurities. The results from the long term studies on commercial lots stored at ICH conditions are sufficient to support storage of bulk drug substance [redacted] with a retest period [redacted].

The drug product, Gilotrif, Afatinib film-coated tablets, contain 40 mg, 30 mg, or 20 mg of afatinib (free base) corresponding to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate. The core excipients contain lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and coated with hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg, and 30 mg tablets only). Tablets are packaged in the [redacted] bottle, closed with a [redacted] screw closure [redacted]. Each bottle contains 30 film-coated tablets for a "unit of use" multi-dose container intended for dispensing directly to the patient.
The manufacturing of drug product involves [redacted] The quality of Afatinib film-coated tablets has been assessed based on its manufacturing process and process controls and found acceptable with respect to analytical procedures for identification, purity, strength, and stability. The tests include: Identification, Assay, Degradation, Dissolution and Uniformity. Based on the submitted stability data on stress and long term study, a 24 months expiry

I concur with the Approval recommendation for this NDA from a CMC perspective.

Ali Al-Hakim, Ph.D.
Branch II Chief, Division I
Office of New Drug Quality Assessment
CDER-FDA
Tel: 301 976 1323

Container Label for the Proposed Drug Product

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/s/

ALI H AL HAKIM
06/27/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 06/07/2013

TO: Carmelo Rosa, Psy.D., Division Director
CDER-Office of Compliance
OMPQ/DIDQ

THROUGH: Patricia Keegan, M.D., Director, Division of Oncology Products 2

FROM: Gideon Blumenthal, M.D. Division of Oncology Products 2

SUBJECT: Statement of medical necessity in support of release of product manufactured in facilities with CGMP Violation.

APPLICATION/DRUG: NDA: 201292/Afatinib

Recommendation

The Division of Oncology Products 2 recommends that the finished product (Afatinib) manufactured with active pharmaceutical ingredient (API) at the finished pharmaceutical manufacturing facility, Boehringer-Ingelheim Pharma GmbH & Co. KG., located at D-55216 Ingelheim am Rhein, Germany be released under regulatory discretion because it serves an unmet medical need in that it provides superior outcomes for a segment of patients with metastatic lung cancer (i.e., those whose tumors bear specific mutations in the epidermal growth factor receptor).

Background: During the November 5-12, 2012 inspection of the facility by the U.S. Food and Drug Administration (FDA) significant violations of current good manufacturing practice (CGMP) for the manufacture of APIs and the CGMP regulations for finished pharmaceuticals were identified. These violations cause APIs and drug product(s) manufactured at the same facility, including afatinib, to be considered adulterated.

Non-Small Cell Lung Cancer (NSCLC) remains the leading cause of cancer deaths in the United States and the world. The 5 year survival rate for patients with NSCLC is approximately 15%. Although surgery remains the only curative modality for this disease, most of these patients (70%) present at advanced stage and thus are not surgical candidates.

Afatinib is an irreversible EGFR tyrosine kinase inhibitor (TKI); mutations in EGFR are present in approximately 10% of non-Asians with NSCLC and are not present in tumors with ALK rearrangements. In a randomized, open-label, adequate and well-controlled study comparing afatinib to platinum-based doublet chemotherapy for the first-line treatment in 345 patients with metastatic, EGFR mutation-positive NSCLC, patients randomized to afatinib experienced a statistically significant and clinically meaningful improvement in progression-free survival (hazard ratio 0.58, p=0.0004) compared to patients treated with chemotherapy, corresponding to a 42% reduction in the immediate risk of tumor progression or death in afatinib-treated patients and an increase in median PFS of 4.2 months, based on the median PFS of 6.9 months for the chemotherapy arm and 11.1 months for the afatinib arm. The overall response rate was also higher for patients randomized to afatinib (56% vs. 23%) than those randomized to chemotherapy. There were no differences in overall survival at an interim analysis; the effects on survival may be obscured by the substantial number of patients in the chemotherapy arm who received post-progression afatinib.

The recommendation to allow the release of the afatinib is based on demonstration of superior efficacy for afatinib as compared to the current standard treatment for the first line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. Currently there is only one drug, erlotinib (Tarceva®, OSI) approved for treatment of NSCLC patients whose tumors contain EGFR mutations. Although erlotinib is approved for this same indication, the drug supply will be considered vulnerable and as there is no assurance of the drug supply, a single alternative will provide an adequate drug supply for this unmet medical need. In addition, certain patients may not tolerate erlotinib and may require treatment with afatinib.

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/s/

DEANNE R VARNEY
06/07/2013

PATRICIA KEEGAN
06/07/2013

MEMO TO FILE

NDA: 201292

From: Li-Shan Hsieh Ph.D.
CMC Reviewer, Branch II, Division I, ONDQA

To: Ali Al-Hakim Ph.D.
Branch Chief, Division I, ONDQA

Date: May 6, 2013

Subject: CMC Amendment to Revise Drug product Specification for Dissolution.

This amendment is to provide revised drug product specifications which the sponsor committed to submit by May 3, 2013 (see CMC review #1).

The revised specification documents provided in this amendment (SD # 35) includes a change to the Q value for dissolution. The specification has been revised (b) (4) to Q = (b) (4) in 15 minutes to address the request made by FDA in the information request dated April 8, 2013. No other content changes have been made to the specification documents.

The content of the analytical procedures remains unchanged. A revised method validation package is also provided in this amendment that includes the changes in document numbering for the drug product analytical procedures

The CMC information is noted and no new action is needed. Therefore, the CMC original recommendation remains the same as documented in CMC review No. 1.

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/s/

LI SHAN HSIEH
05/06/2013

ALI H AL HAKIM
05/06/2013

NDA 201292

Gilotrif® (Afatinib) Tablets

Boehringer Ingelheim Pharmaceuticals, Inc.

Li-Shan Hsieh, Ph. D.

Review Chemist

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

CMC REVIEW OF NDA 201292
For the Office of Hematology and Oncology Drug Products
Division of Oncology Drug Products 2

Table of Contents

CMC Review Data Sheet

1. NDA 201292

2. REVIEW #: 1

3. REVIEW DATE: 19-Apr-2013

4. REVIEWER: Li-Shan Hsieh, Ph. D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-IND meeting	29-Sep-2003
Original IND 67969 submission	30-Dec-2003
Original IND 67969 CMC review	Not reviewed
IND 67969 (SD 496 and 544)	08-Jun-2010
CMC included pre-NDA meeting	15-Dec-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	15-Nov-2011	15-Nov-2011
Amendment (Response to 13-Dec-2012 IR)	6	04-Jan-2013	04-Jan-2013
Amendment (Response to Biopharm 08-Apr-2013 IR)	33	11-Apr-2013	11-Apr-2013
Amendment (Propriety name)	23	04-Mar-2013	04-Mar-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Address: 4001 Miranda Ave, Palo Alto, CA 94304

Representative: Ann Agnor, MS, Associate Director, Regulatory Affairs
Telephone: 230-798-5345, Fax: 230-791-6252

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Gilotrif
b) Non-Proprietary Name: Afatinib dimaleate
c) Code Name/# (ONDQA only): BIBW 2992 MA2

CMC Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: *ErbB* Family of receptor tyrosine kinase Inhibitor

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 20 mg, 30 mg, 40 mg, (b) (4)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

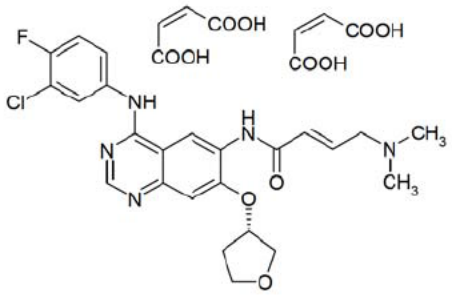
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√__ Not a SPOTS product

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

2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-(2E)-, (2Z)-2-butenedioate (1:2)



Molecular Formula: $C_{24}H_{25}ClFN_5O_3 \cdot 2\ C_4H_4O_4$ or $C_{32}H_{33}ClFN_5O_{11}$
Molecular Weight: 718.1 g/mol (salt form), 485.9 g/mol (free base)

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	LoA date
(b) (4)				3			06-Jul-2011
				3			20-Sep-2011
				3			10-Jul-2006
				3			20-Sep-2010
				3			09-Sep-2010

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")

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67969	
CDRH PMA	(b) (4)	Qiagen Therascreen® EGFR RGO PCR kit

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approval	22-Apr-2012	Jonathan Norton
EES	pending	17-Apr-2013	Lauren C Iacono-Connors
Pharm/Tox	Acceptable	19-Apr-2012	Dubravka Kufrin
Biopharm	Approval	22-Apr-2013	Elthbeth G Chikhale
LNC	N/A		
Methods Validation Requested	Submitted		
DMEPA*	Acceptable	19-Apr-2013	James H Schlick
EA	Categorical exclusion (see review)	19-Apr-2013	Li-Shan Hsieh
Microbiology	N/A		
CDRH consult	N/A		

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 201292

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from Chemistry Manufacturing and Control perspective. However, this recommendation does not take into consideration, the status of the cGMP status of the manufacturing site(s)which is currently pending

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

Afatinib (free base) or Afatinib dimaleate (salt form) is a chemically synthesized small molecule and is a white to brownish yellow powder. Afatinib is highly soluble in water and is hygroscopic. (b) (4)

(b) (4)

The synthetic process has been optimized during development to improve the robustness of the process, the quality of intermediates and the drug substance. Potential impurities and degradants are identified and eliminated as appropriately.

The release specification and analytical procedures are described in sufficient detail and validated for its intended use. Criteria are justified by batch analysis data and non-clinical studies. Reference standards have been established for drug substance and potential impurities. Stability information includes stress and long term studies. The results from the long term studies on commercial lots stored at ICH conditions are sufficient to support storage of bulk drug substance (b) (4) (b) (4) with a retest period (b) (4)

(2) Drug Product

Gilotrif, Afatinib film-coated tablets, contain 40 mg, 30 mg, or 20 mg of afatinib (free base) corresponding to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate. The originally proposed [redacted]. The core excipients contain lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and coated with hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg, and 30 mg tablets only). These film-coated tablets is debossed with the strength code "T20", "T30", or "T40" and the other side with the Boehringer Ingelheim company symbol. Tablets are packaged in the [redacted] bottle, closed with a [redacted] screw closure [redacted]. Each bottle contains 30 film-coated tablets for a "unit of use", multi-dose container intended for dispensing directly to the patient.

The manufacturing of drug product involves [redacted] The quality of Afatinib film-coated tablets has been assessed based on its manufacturing process and process controls; the analytical procedures for identification, purity, strength, and stability. The tests include: Identification, Assay, Degradation, Dissolution and Uniformity. Based on the submitted stability data on stress and long term study, a 24 months expiry period has been accepted with storage at controlled room temperature.

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

Treatment of patients with locally advanced or metastatic non-small cell lung cancer with epidermal growth factor

C. [redacted] Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant.

All drug substance and drug product manufacturing, packaging and control facilities were submitted to EES. An overall recommendation is pending.

III. Administrative

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

Li-Shan Hsieh, Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Liang Zhou, CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Ali H. Al Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

LI SHAN HSIEH
04/22/2013

ALI H AL HAKIM
04/22/2013
I concur.

Filling Template

NDA Number: 201-292 **Supplement Number and Type:** **Established/Proper Name:** Afatinib

Applicant: Boehringer Ingelheim Pharm., Inc. **Letter Date:** 14 November, 2012 **Stamp Date:** 15 November, 2012

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

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	Yes		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Yes		This is review issue.

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

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

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

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

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

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

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

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

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

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

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

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

{Haripada Sarker *12-11-2012*

CMC Lead
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

Date

{Nallaperumal Chidambaram} *12-12-2012*

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

Date

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

/s/

HARIPADA SARKER
12/12/2012
Filing review on behalf of Liang Zhou.

NALLAPERUM CHIDAMBARAM
12/12/2012