

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203469Orig1s000

CHEMISTRY REVIEW(S)

NDA 203-469

**ICLUSIG
(ponatinib) tablets
15 and 45 mg
ARIAD Pharmaceuticals, Inc.**

Division of Oncology Drug Products

**Donghao (Robert) Lu, Ph.D (Drug Substance)
Amit K. Mitra, Ph.D (Drug Product)**

Branch II/ONDQA

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Chemistry Review Data Sheet

1. NDA 203-469
2. REVIEW #: 1
3. REVIEW DATE: 19 NOVEMBER 2012
4. REVIEWER: Donghao (Robert) Lu, Ph.D. and Amit K. Mitra, Ph.D
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

30-JUN-2012

Amendment

12-OCT-2012

Amendment

07-NOV-2012

Amendment

14-NOV-2012

Amendment

19-NOV-2012

7. NAME & ADDRESS OF APPLICANT:

Name: ARIAD Pharmaceuticals, Inc.

Address: 26 Landsdowne Street. Cambridge, MA 02139

Representative: Daniel Bollag

Telephone: 617-494-0400

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Iclusig
b) Non-Proprietary Name (USAN): Ponatinib hydrochloride
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only): AP24534 Hydrochloride, AP24534 HCl
- Chem. Type: 1
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 15 and 45 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

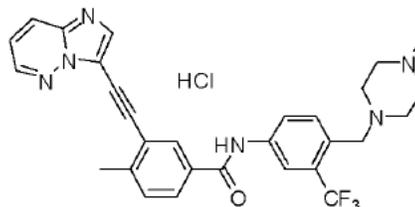
Not a SPOTS product

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

Name, INN: Ponatinib
Name, USAN: Ponatinib Hydrochloride
Name (CAS): Benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl) methyl]-3-(trifluoromethyl)phenyl]-, hydrochloride (1:1)
Name (IUPAC): 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride
Company Code: AP24534 Hydrochloride, AP24534 HCl, FP0070
(CAS) Registry Num: 1114544-31-8 (HCl salt), 943319-70-8 (free base)
Mol. Formula: C₂₉H₂₈ClF₃N₆O (HCl salt), C₂₉H₂₇F₃N₆O (free base)
Mol. Wt.: 569.02 g/mol (HCl salt), 532.56 g/mol (free base)

Chemistry Review Data Sheet

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	21-SEP-2011	See Chemistry Review #1 by Dr. D.E. Woods
	III	(b) (4)	(b) (4)	4	Adequate		Sufficient information in the NDA for the (b) (4)
	III	(b) (4)	(b) (4)	4	Adequate		Sufficient information in the NDA application for the (b) (4)
	III	(b) (4)	(b) (4)	4	Adequate		Sufficient information in the application for bottles
	III	(b) (4)	(b) (4)	4	Adequate		Sufficient information in the NDA application for bottles
	III	(b) (4)	(b) (4)	4	Adequate		Sufficient information in the NDA application for bottles
	III	(b) (4)	(b) (4)	4	Adequate		Sufficient information in the NDA application for bottles
	III	(b) (4)	(b) (4)	4	Adequate		Sufficient information in the NDA application for bottles

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	3	Adequate	24-APR-2012	See Review #4 by Dr. G. Lunn
	III		4	Adequate		Sufficient information in the NDA application for bottles
	III		4	Adequate		Sufficient information in the NDA application for bottles
	III		4	Adequate		Sufficient information in the NDA application for bottles
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	III		4	Adequate		Sufficient information in the NDA application for bottles

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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78375	15 and 45 mg film coated tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Satisfactory	07-NOV-2012	Mr. D. Smith
Pharm/Tox	Acceptable	16-OCT-2012	Dr. S. Ricci
Biopharm	Acceptable	19-NOV-2012	Dr. K. Riviere
LNC	Satisfactory		
Methods Validation	Acceptable for Drug substance section. A modification of ID, Assay and Impurities method for drug product was recommended by the FDA methods validation laboratory. The applicant made a post-approval commitment to address this issue. See Section B under recommendation section below.	06-NOV-2012	Dr. M. Trehy
DMEPA	Trade name satisfactory	20-AUG-2012	Mr. S. K. Vee
EA	Satisfactory		Dr. A. K. Mitra
Microbiology	Satisfactory	24-OCT-2012	Mr. S. P. Donald

The Chemistry Review for NDA 203-469

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ponatinib hydrochloride drug product is recommended for APPROVAL from the standpoint of chemistry, manufacturing and controls.

Include the following language in the action letter:

Based on the provided stability data, an expiration dating period of 12 months is granted for the drug product when stored at 25°C (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 applicant made the following post approval agreement. ARIAD will submit the updated method "*Identification, Content Uniformity, Assay and Impurities Method for Ponatinib (AP24534) Tablets, 15mg and 45 mg*" (AM1281) post approval, minimally within 3 months, to the application via a Supplement, Changes Being Effected – 30 Days (CBE-30). The method validation remains unchanged and is current in the Application

II. Summary of Chemistry Assessments

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

1. Drug Substance

The drug substance is ponatinib hydrochloride. The chemical name is 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl) phenyl}benzamide hydrochloride. It has a molecular formula of C₂₉H₂₈ClF₃N₆O and its molecular weight is 569.02.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route and the use of reagents are adequate for the manufacturing of ponatinib hydrochloride drug substance. As this is a new molecular entity, a methods validation request was sent (subsequently determined to be acceptable) for the HPLC method for the determination of assay and organic impurities.

The impurities detected during the development of the drug substance were evaluated. Analytical methods were developed for the control of the impurities

Chemistry Assessment Section

listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level was adequately presented.

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

2. Drug Product

The proposed commercial ponatinib drug product is an immediate release film coated tablets at two different strengths. The 15 mg tablet is described as: “white ¼ inch (6.35 mm) round film-coated tablets, debossed “A5” on one side and plain on the other side”. The 45 mg tablet is described as: “white 3/8 inch (9.53 mm) round film coated tablets, de-bossed “AP4” on one side and plain on the other side”.

The core tablets of the two product strengths are proportional in composition. The tablets contain a nominal 15 mg or 45 mg of the active ingredient, ponatinib free base, provided as ponatinib HCl. The inactive components of tablets are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, Type B, colloidal silicon dioxide, magnesium stearate, and (b) (4) white film coating which contains talc, polyethylene glycol, polyvinyl alcohol and titanium dioxide. 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 formulation and manufacturing process have changed over the course of product development with only 3 dosage forms/formulations administered in clinical studies: Drug in capsule (2 mg), capsules (5 and 15 mg) and film coated tablets (15 and 45 mg). The core tablet formulation was developed using some elements of Quality by Design. However, the regulatory dissolution method was not used in determination of the response and a complete linkage of raw material attributes and the process parameters to product quality was not achieved. The film coating process was developed using (b) (4). The applicant submitted 12 months long term stability data with the submission. During stability studies, the applicant, changed the dissolution method at the 12 months time point. Also, during the course of development, the applicant chose to commercialize the drug product from a different facility than that of the developmental facility. There were minor variations in the manufacturing process parameters also. But overall, all manufacturing process steps remained the same. The applicant provided 3 months stability data and dissolution information to bridge the commercial site

Chemistry Assessment Section

to the developmental site. Details of the bridging information by f2 test are documented in the Biopharmaceutics review. Based on the limited stability data from the commercial site, a shelf life of 12 months is recommended by the reviewer and the applicant agreed to the 12 months tentative shelf life.

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

The drug product is proposed to be marketed in 60 and 180 counts for 15 mg tablets, and 30 and 90 counts for the 45 mg tablets. Both strengths are packaged in high density bottles.

The applicant has provided sufficient stability data for a 12 months tentative shelf life under long term storage conditions. The storage conditions are described as follows: Store at controlled room temperature 20-25°C (68° to 77° F); excursions permitted between 15° to 30° C (59° to 86°F).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has responded satisfactorily to all Information Request letters. The Office of Compliance has provided an overall acceptable recommendation. Based on the above, this application is recommended for approval from the standpoint of chemistry, manufacturing and controls.

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

\s\ Donghao (Robert) Lu, Ph.D. Chemistry Reviewer
\s\ Amit K. Mitra, Ph.D, Chemistry Reviewer

B. Endorsement Block

\s\ Nallaperumal Chidambaram, Branch Chief (Acting)

C. CC Block

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/s/

DONGHAO R LU
11/20/2012

AMIT K MITRA
11/20/2012
Drug Product reviewer

NALLAPERUM CHIDAMBARAM
11/20/2012
I concur.

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

METHODS VALIDATION REPORT SUMMARY

TO: Donghao (Robert) Lu, CMC Reviewer
Amit Mitra, DP CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Donghao.Lu@fda.hhs.gov ; Amit.Mitra@fda.hhs.gov
Phone: (301) 796-2059; (301) 796-1420

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, Ph.D., MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

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

SUBJECT: Methods Validation Report Summary

Application Number: 203469

Name of Product: Ponatinib Tablets

Applicant: Ariad Pharmaceuticals, Inc.

Applicant's Contact Person: Andrew Slugg, Director, Regulatory Affairs

Address: 526 Landsdowne Street, Cambridge, MA 02139

Telephone: (617) 503-7097 Fax: (617) 225-2688

Date Methods Validation Consult Request Form Received by DPA: 8/16/12

Date Methods Validation Package Received by DPA: 8/16/12

Date Samples Received by DPA: 9/11/12

Date Analytical Completed by DPA: 11/6/12

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

Comments: Sample results summary and method comments are in attached memo.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

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

Date: November 5, 2012
To: Donghao (Robert) Lu, CMC Reviewer, Office of New Drug Quality Assessment
Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis
From: Wei Ye, Chemist
Subject: Method Validation for NDA 203469
Ponatinib Tablets
Ariad Pharmaceuticals, Inc.

The following method was evaluated and is acceptable for quality control and regulatory purposes:

HPLC Analysis of (b) (4) (Ariad Pharmaceuticals, Inc., Document Number: TM0921-00, Page 1 of 17)

The following method was evaluated and is acceptable for quality control and regulatory purposes with modification:

Identification, Content Uniformity, Assay and Impurities Method for Ponatinib (AP24534) Tablets, 15 mg and 45 mg (Ariad Pharmaceuticals, Inc., Document Number: AM1281, Revision 06, Page 1 of 14)

The Division of Pharmaceutical Analysis has the following comment pertaining to this method.

(b) (4)

(b) (4)



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/s/

MICHAEL L TREHY
11/05/2012

BENJAMIN J WESTENBERGER
11/06/2012

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Product Quality and Manufacturing Memo

Memo Date: October 10, 2012
From: Amit K. Mitra, Ph.D
Donghao Lu, Ph.D
on behalf of the CMC Review Team

Through: Nallaperumal Chidambaram, Ph.D Branch Chief, Division I

NDA Number: 203-469 GRMP Date: 25-OCT-2012 (Review)
Applicant: Ariad Pharmaceuticals LLC PDUFA Date: 15-NOV-2012

Drug Product Name and Strength: Iclusig (ponatinib) tablets, 15 and 45 mg

Drug Product Introduction:

The 15 mg and 45 mg ponatinib film coated tablets are round, white film coated, biconvex tablets debossed with "A5 for 15 mg or AP4 for 45 mg" on one side and plain on the other.

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

The drug product is packaged in high density polyethylene (HDPE) bottles containing desiccant with induction seal and child-resistant closures  (b) (4)

Drug Substance Introduction:

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/s/

AMIT K MITRA
10/12/2012

DONGHAO R LU
10/12/2012

NALLAPERUM CHIDAMBARAM
10/12/2012

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

OND Division: Division of Hematology Products
NDA: 203469
Applicant: ARIAD Pharmaceuticals, Inc.
Stamp Date: 30-Jul-2012
PDUFA Date: Priority (Expedited)
Proprietary (Brand) Name of Drug Product: Iclusig (ponatinib) tablets
Established Name: Ponatinib tablets
Dosage Form(s): Film-coated tablet
Strength(s): 15 mg, 45 mg
Route of Administration: Oral
Proposed Indication(s): Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy
CMC Lead: Janice Brown, Branch II/DNDQA1/ONDQA
Chief, Branch II: Nallaperumal Chidambaram, DNDQA1/ONDQA
Review team recommendation: Team review
 CMC reviewers: Amit Mitra, Donghao (Robert) Lu
 Biopharm reviewer: Kareen Riviere

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

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
Biopharm	Kareen Riviere
CDRH	Not Applicable for drug product; (b) (4) (b) (4)
EA	Categorical Exclusion requested
EES	Inspection request was submitted on 01-Oct-2012
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	Requested on 16-Aug-2012
Microbiology	Steven Donald
Pharm-Tox	Determined by primary reviewer.

SUMMARY

Ponatinib (AP24534) is a new molecular entity indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy.

Ponatinib is an orally-available tyrosine kinase inhibitor (TKI). The primary target of ponatinib is BCR-ABL, an abnormal tyrosine kinase that is the hallmark of chronic myeloid leukemia (CML) and Ph+ ALL. The fusion protein product of the Philadelphia chromosome (Ph), BCR-ABL, is a constitutively active tyrosine kinase that gives rise to chronic myeloid leukemia (CML). [REDACTED] (b) (4)

Ponatinib was designed using ARIAD's computational and structure-based drug design platform to inhibit the enzymatic activity of BCR-ABL. The agent was intended to target not only native BCR-ABL, but also BCR-ABL isoforms that carry mutations conferring resistance to treatment with existing TKIs, including the T315I mutation which cause resistance to all approved BCR-ABL TKIs for which no effective therapy exists.

During the course of clinical development of ponatinib, patients were tested for the presence of the T315I BCR-ABL mutation by [REDACTED] (b) (4) conducted by a single central laboratory, [REDACTED] (b) (4) has developed an in vitro diagnostic test for the detection of BCR-ABL T315I mutation. [REDACTED] (b) (4)

This NDA is a rolling submission with essentially a complete module 3 including 12 month data for 6 primary drug product stability lots (3 x 15 mg, 3 x 45 mg). The second part of the submission includes 3 month data on 4 lots of 15 mg and 3 lots of 45 mg for drug product batches produced at the proposed commercial [REDACTED] (b) (4) manufacturing facility, release data for 15 mg and 45 mg drug product process validation lots, drug product photostability test data, and comparability assessment of drug product manufactured at [REDACTED] (b) (4) and new [REDACTED] (b) (4) commercial facility.

The initial submission included both HDPE bottles [REDACTED] (b) (4) for ponatinib tablets (see table 11). One 45 mg lot (lot 260265) manufactured at the new [REDACTED] (b) (4) facility failed dissolution testing [REDACTED] (b) (4)

Ponatinib received orphan drug designation under section 526 of the FD&C Act for the treatment of CML and Ph+ALL on 20 November 2009.

Fast Track designation was granted on 30 November 2010.

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/s/

JANICE T BROWN
10/03/2012

NALLAPERUM CHIDAMBARAM
10/04/2012

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	203-469
Submission Date	7/30/2012; 9/27/2012
Product name, generic name of the active	Iclusig® (ponatinib) Tablets
Dosage form and strength	IR Tablets/ 15 mg and 45 mg
Indication	Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to prior tyrosine kinase inhibitor therapy
Applicant	Ariad Pharmaceuticals, Inc.
Clinical Division	DHP
Type of Submission	Original 505(b)(1) New Drug Application
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

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

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Is the dissolution test part of the DP specifications?	x		
2.	Does the application contain the dissolution method development report?	x		
3.	Is there a validation package for the analytical method and dissolution methodology?	x		
4.	Does the application include a biowaiver request?		x	Not Applicable.
5.	Is there information provided to support the biowaiver request?		x	Not Applicable.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant claims that (b) (4) is a BCS Class 2 drug substance.
8.	Is information on mixing the crushed product with foods or liquids included?		x	Not Applicable.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

9.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		PK data from dose escalation, food effect, drug-drug interaction, and ADME studies were included in the submission (these data will be reviewed by OCP).
10.	Does the application contain QbD elements?	x		This submission has QbD elements for drug substance and product manufacturing.
11.	Is dissolution used to support the proposed design space(s)?	x		Dissolution is used as a response parameter in the selection of the proposed formulation ^{(b) (4)} design spaces for the tablet formulation.

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
12.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
13.	If the NDA is not fileable from the Biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	
14.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		IR comments were sent to the Applicant prior to a filing action. The comments are outlined in the Attachment.

{See appended electronic signature page}

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

10/3/2012
Date

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

10/3/2012
Date

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

ATTACHMENT

Biopharmaceutics Information:

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method and acceptance criterion as well as dissolution data supporting the drug product manufacturing site change. This submission has Quality by Design elements for drug substance and product manufacturing.

In early clinical development, a capsule formulation was studied in phase 1 studies. A tablet formulation (15 mg and 45 mg strengths) that is also the to-be-marketed formulation was subsequently developed and tested in a phase 2 pivotal efficacy and safety clinical trial. In addition, the pharmacokinetics of both strengths of the to-be-marketed tablet formulation were evaluated, and therefore, provides the basis for bridging between the phase 1 and 2 studies.

The proposed dissolution method:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
1	50 rpm	900 mL	37°C	HCl/KCl pH 2.1 buffer

The proposed acceptance criterion:

Acceptance Criterion
$Q = \frac{(b)}{(4)}\% \text{ at } \frac{(b)}{(4)} \text{ minutes}$

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology, the proposed dissolution acceptance criterion, and the dissolution data supporting the drug product manufacturing site change, as well as the role of dissolution as a response parameter in the selection of the proposed formulation (b) (4) design spaces for the tablet formulation.

To facilitate the review of the Applicant's submission, the following comments were conveyed to the Applicant in an IR letter dated September 20, 2012:

1. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for your proposed product.
2. In the formulation DoE studies, dissolution was identified as a response variable. However, the proposed dissolution method (Dissolution Method-2) was not used to assess the impact of formulation changes on dissolution. Additionally, the dissolution method used (Dissolution Method-1) is not acceptable because it is not discriminating. Thus, the provided dissolution data cannot be used to support the formulation design space. (b) (4)

(b) (4) This percent change is considered a major change which requires additional supporting data beyond dissolution profiles comparisons (e.g. BA/BE studies). Discuss how bioequivalence is assured upon the proposed ranges in these excipient

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

levels in your formulation design space. If available, provide the data from an *in vivo* bioequivalence study demonstrating that the formulations manufactured with these ingredients at the following extreme levels are bioequivalent. Additionally, provide the *in vitro* comparative dissolution profile data, using the proposed dissolution method, and similarity f2 values demonstrating that the formulations manufactured with these ingredients at the following levels have similar dissolution rate. If no *in vivo* data are available, the formulation design space should be restricted to changes in formulations comparable to a Level 2 change under SUPAC (b) (4)

3. In the (b) (4) DoE studies, dissolution was a response variable. However, the proposed dissolution method (Dissolution Method-2) was not used to assess the impact of (b) (4) parameters on dissolution. Additionally, the dissolution method used (Dissolution Method-1) is not acceptable because it is not discriminating. Thus, the provided dissolution data cannot be used to support the (b) (4) design space. In order to support the (b) (4) design space, provide the *in vitro* comparative dissolution profile data, using the proposed dissolution method, and similarity f2 values demonstrating that the proposed drug product manufactured with press setting variables at the proposed ranges have similar dissolution rate.

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/s/

KAREEN RIVIERE
10/03/2012

SANDRA SUAREZ
10/03/2012

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

NDA Number:	Supplement Number and Type:	Established/Proper Name:
203469	Original NDA	Ponatinib tablets
Applicant:	Letter Date:	Stamp Date:
ARIAD Pharmaceuticals, Inc	27-Sep-2012	27-Sep-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?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

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

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
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: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

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

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

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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	X		
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			Refer to Biopharm filing review
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Expiry will be determined by primary reviewers in ONDQA
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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

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

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?	X		

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

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

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

{See appended electronic signature page}

Janice Brown
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 28-Sep-2012

{See appended electronic signature page}

Nallaperumal Chidambaram, Ph.D.
Chief, Branch 2 (Acting)
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 28-Sep-2012

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/s/

JANICE T BROWN
09/28/2012

NALLAPERUM CHIDAMBARAM
09/28/2012

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

METHODS VALIDATION CONSULT REQUEST FORM

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

FROM: Donghao (Robert) Lu, CMC Reviewer
Amit Mitra, DP CMC Reviewer
Kareen Riviere, Biopharm Review
Janice Brown, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Donghao.Lu@fda.hhs.gov; Amit Mitra@fda.hhs.gov
Phone: (301)-301-796-2059; 301-796-1420
Fax.: (301)-CMC Reviewer's FAX number

Through: Nallaperum Chidambaram, Acting Chief Branch 2
Phone: (301)-796-1339

and

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

SUBJECT: Methods Validation Request

Application Number: NDA 203469

Name of Product: Ponatinib Tablets

Applicant: Ariad Pharmaceuticals, Inc.

Applicant's Contact Person: Andrew Slugg, Director, Regulatory Affairs (andrew.slugg@ariad.com)

Address: 526 Landsdowne Street , Cambridge, MA 02139

Telephone: (617)503-7097 Fax: (617) 225-2688

Date NDA Received by CDER: **7/30/2012**
NME

Submission Classification/Chemical Class:

Date of Amendment(s) containing the MVP:

Special Handling Required: Yes

DATE of Request: **August 16, 2012**

DEA Class: N/A

Requested Completion Date: **10/16/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **11/15/2012**

Paper Electronic Mixed

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

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the

laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 203469
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
TM0921	DS - Assay and Impurities	3.2.S.4.2	0	
AM1281	DP - Assay and Impurities	3.2.P.5.3	0	
<p>Additional Comments: This NDA has been classified as a priority review; however, the review timeline has been expedited. The action date has been changed to November 15, 2012.</p> <p>Note that this is a cytotoxic drug and should be handled appropriately.</p>				

Methods Validation Request Criteria

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

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/s/

JANICE T BROWN
08/16/2012

NALLAPERUM CHIDAMBARAM
08/16/2012
I concur

JEANNIE C DAVID
08/16/2012
ONDQA Methods Validation Project Manager