

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203341Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203341

SUPPL #

HFD # 160

Trade Name BOSULIF® Tablets, 100 mg and 500 mg.

Generic Name bosutinib

Applicant Name Wyeth Pharmaceuticals, Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
YES  ! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: CDR Diane Hanner

Title: Regulatory Project Manger

Date: August 24, 2012

Name of Office/Division Director signing form: Ann T. Farrell, M.D.,

Title: Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANE C HANNER  
08/24/2012

ANN T FARRELL  
09/04/2012

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 203341 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DHP PDUFA Goal Date: \_\_\_\_\_ Stamp Date: Nov. 17, 2011  
Sept 19, 2012

Proprietary Name: BOSULIF®

Established/Generic Name: bosutinib

Dosage Form: Tablets, 100 mg and 500 mg.

Applicant/Sponsor: Wyeth Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) For the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy.

(2) \_\_\_\_\_

(3) \_\_\_\_\_

(4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** For the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy.

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
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Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

*additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_

**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)  
 No: Please check all that apply:  
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)  
 Deferred for some or all pediatric subpopulations (Complete Sections C)  
 Completed for some or all pediatric subpopulations (Complete Sections D)  
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)  
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)  
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A:</b> Fully Waived Studies (for all pediatric age groups)
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Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:  
 Disease/condition does not exist in children  
 Too few children with disease/condition to study  
 Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

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/s/  
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DIANE C HANNER  
08/23/2012

**NDA 203341**

**Bosutinib Monohydrate**

**DEBARMENT CERTIFICATION**

**[FD&C Act 306(k)(1)]**

Wyeth, Inc., a wholly owned subsidiary of Pfizer, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

**Carl M. DeJuliis**

Digitally signed by Carl M. DeJuliis  
DN: cn=SAFE Signatures,  
ou=M818456and62031469689904306715066066, c=Carl M.  
DeJuliis  
Reason: I attest to the accuracy and integrity of this document.  
Location: Groton, CT  
Date: 2011.11.07 15:29:32 -05'00'

11/07/2011

---

Carl M. DeJuliis

---

Date

PFIZER CONFIDENTIAL

**Hanner, Diane**

**From:** Hanner, Diane  
**Sent:** Tuesday, August 28, 2012 10:47 AM  
**To:** 'Dejuliis, Carl M'  
**Subject:** FW: USPI\_PPI-Bosulif-bosutinib-tablets NDA 203341  
**Importance:** High

Hi Carl,  
I need to inform you of the following regarding the NDA 203341 (Bosutinib) label:

"We do not agree with the addition of the [REDACTED] (b) (4)

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

---

**From:** Dejuliis, Carl M [<mailto:carl.m.dejuliis@pfizer.com>]  
**Sent:** Monday, August 27, 2012 3:39 PM  
**To:** Hanner, Diane  
**Subject:** RE: USPI\_PPI-Bosulif-bosutinib-tablets NDA 203341

Hi Diane

Upon final review, we would like to add some language to Section 6.2 (see the proposed addition in red below):

Gastrointestinal Disorders: *1% and less than 10%* - gastritis; *0.1% and less than 1%* - acute pancreatitis, gastrointestinal hemorrhage [REDACTED] (b) (4)

**RATIONALE:**

[REDACTED] (b) (4)  
In order to provide as much useful information to the treating physician as possible, we propose to add this information.

Is this acceptable to the FDA? If so, we concur with the proposed insert, as revised (please see the attached).

Thank You,

Warmest Regards,

Carl M. DeJuliis, Pharm D

Pfizer, Inc

MS 8260-1123

445 Eastern Point Road

Groton, Ct 06340

Office Phone: 860-441-1693

(b) (6)

[carl.m.dejuliis@pfizer.com](mailto:carl.m.dejuliis@pfizer.com)

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/s/  
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DIANE C HANNER  
08/28/2012

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Wednesday, August 08, 2012 5:31 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** RE: NDA 203341 Bosutinib Container labeling comments

Hi Carl,  
Yes, it is acceptable to keep [see USP Controlled Room Temperature] on both bottle and PI.  
Regards,  
Diane

---

**From:** Dejuliis, Carl M [mailto:carl.m.dejuliis@pfizer.com]  
**Sent:** Tuesday, August 07, 2012 6:37 PM  
**To:** Hanner, Diane  
**Subject:** RE: NDA 203341 Bosutinib Container labeling comments

Hi Diane,

For item 1, we will keep "tablets" bolded and agree to use the same font type for the generic name. We agree with changes 2, 3, 4, and 5 and your acceptance for our proposal for item 6.

**Question**

The bottle is labeled as

Store at room temperature 20°C to 25 °C (68°F to 77 °F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

When we received the Draft PI from you in section 16.2 [see USP Controlled Room Temperature] was deleted. We wish to keep [see USP Controlled Room Temperature] on the package insert to maintain consistency with the bottle. We have already added back in the draft insert with our response to your comments.

Is it acceptable to keep [see USP Controlled Room Temperature] both on the bottle label and PI?

Thank you ,

Warmest Regards,

Carl M. DeJuliis, Pharm D  
Pfizer, Inc  
MS 8260-1123  
445 Eastern Point Road  
Groton, Ct 06340  
Office Phone: 860-441-1693

(b) (6)

[carl.m.dejuliis@pfizer.com](mailto:carl.m.dejuliis@pfizer.com)

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**From:** Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]  
**Sent:** Tuesday, August 07, 2012 4:59 PM  
**To:** Dejuliis, Carl M  
**Subject:** RE: NDA 203341 Bosutinib Container labeling comments

Hi Carl,  
Please let me know if you will be responding to soon regarding the container labeling information below.  
Thanks.  
Regards,  
Diane

---

**From:** Hanner, Diane  
**Sent:** Friday, July 27, 2012 2:22 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** RE: NDA 203341 Bosutinib Container labeling comments

Hi Carl,  
I have the following to report to you regarding the NDA 203341 Bosutinib Container (please see the container information below in red).  
Regards,  
Diane

---

**From:** Dejuliis, Carl M  
**Sent:** Wednesday, July 11, 2012 10:24 AM  
**To:** 'Hanner, Diane'  
**Subject:** RE: NDA 203341 Bosutinib Container labeling comments

Hi Diane,

We have some comments regarding points 1 and 6 (see below in Red) for your consideration. Thank you.

Warmest Regards,

Carl M. DeJuliis, Pharm D  
Pfizer, Inc  
MS 8260-1123  
445 Eastern Point Road  
Groton, Ct 06340  
Office Phone: 860-441-1693  
 (b) (6)  
[carl.m.dejuliis@pfizer.com](mailto:carl.m.dejuliis@pfizer.com)

**From:** Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]  
**Sent:** Tuesday, July 10, 2012 9:41 AM  
**To:** DeJuliiis, Carl M  
**Subject:** NDA 203341 Bosutinib Container labeling comments  
**Importance:** High

Hi Carl,

Please note the container labeling comments below regarding NDA 203341 (Bosutinib):

A. Container Labels (100 mg and 500 mg trade bottle)

1. Unbold the dosage form "tablets". Additionally, ensure the established name (which consists of the active ingredient plus the dosage form) has prominence commensurate with the prominence of the proprietary name, including typography (size, font, etc.), layout, contrast, and other printing features, as per 21 CFR 201.10(g)(2).

**Pfizer tries to maintain consistency in their packaging by following corporate packaging guidelines that are in line with FDA labeling regulations. The bolding of the dosage form is one element in these guidelines and has been followed for other recent Pfizer product approvals by FDA (ie: Xalkori and Inlyta). We wish to maintain the bold font type for the dosage form in an effort to provide a consistent presentation of our products to our customers. Is this acceptable to the Agency?**

**FDA Response: We agree to your proposal of using the bold font type for the dosage form "tablets" if you agree to use the same font type for the active ingredient of the product "bosutinib" - as you have done with Inlyta. Alternatively, you may retain the current unbolded font type for the active ingredient "bosutinib" and unbold the dosage form "tablets".**

2. Add the statement "Do not crush or cut tablet" on the front principal display panel.
3. Add the statement "For Oncology Use Only" on the front principal display panel.
4. Change the wording on the Storage condition statement to read "Store at 20°C to 25°C (68°F to 77°F); excursions..." rather than "Store at 25°C (77°F); excursions..."
5. Ensure that the expiration date and lot number is printed on each container label, as per 21 CFR 201.17 and 21 CFR 201.18. It is unclear from the label images submitted whether there is a placeholder for this information.
6. Revise "MADE IN SPAIN" to

(b) (4)

(b) (4)

**Pfizer does not agree to the request**

(b) (4)

**The statement "MADE IN SPAIN" is included on the label to comply with the country of origin requirements of US Customs law (19 CFR 134.11). This statement is**

determined by US Customs rules and is based on the source of the API and other factors, and is required for the label.

(b) (4)

21 CFR Section 201.1 requires that the label include the name of the manufacturer, packer or distributor. The Bosulif label complies with this regulation because it bears the statement "Distributed by Pfizer Labs, Division of Pfizer Inc."

Based on the above information, is it acceptable to the Agency not to make this change?

**FDA Response: The proposal is acceptable.**

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
08/08/2012

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Tuesday, August 07, 2012 4:42 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** FW: NDA 203341 Bosutinib DRAFT Labeling and DRAFT PMR

Hi Carl,  
The FDA response to your inquiry is below:

- Erythromycin was provided as an example in the PMR, but another moderate inhibitor may be appropriate. You may specify the moderate inhibitor you plan to use when you submit your study protocol.

Regards,  
Diane

---

**From:** Dejuliis, Carl M [mailto:carl.m.dejuliis@pfizer.com]  
**Sent:** Monday, August 06, 2012 4:10 PM  
**To:** Hanner, Diane  
**Subject:** RE: NDA 203341 Bosutinib DRAFT Labeling and DRAFT PMR

Hi Diane,

Attached are our comments on the DRAFT NDA Labeling, except for Section 14. Section 14 to follow.

PMR

We agree with the initial due dates specified by FDA. However, since erythromycin and bosutinib have overlapping GI toxicities, we would like to use aprepitant or another moderate CYP3A inhibitor in the study.

Please let me know when you receive this or if you have another questions.

Thank You,

Warmest Regards,

Carl M. DeJuliis, Pharm D  
Pfizer, Inc  
MS 8260-1123  
445 Eastern Point Road  
Groton, Ct 06340  
Office Phone: 860-441-1693  
(b) (6)  
[carl.m.dejuliis@pfizer.com](mailto:carl.m.dejuliis@pfizer.com)

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**From:** Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]  
**Sent:** Monday, July 30, 2012 4:31 PM  
**To:** Dejuliis, Carl M  
**Subject:** NDA 203341 Bosutinib DRAFT Labeling and DRAFT PMR  
**Importance:** High

Hi Carl,

As promised, attached please find the DRAFT NDA 203341 Bosutinib Labeling which includes all of the sections, except Section 14. Please be informed that these sections are still considered to be in "DRAFT" form, and we may

have additional changes forthcoming!

Also, below I'm including the initial draft PMR Language for your consideration. Please let me know if you agree with the initial due dates.

Thank you.

Regards,

Diane

PMR Description:	Conduct a drug-drug interaction trial to evaluate the effect of a moderate CYP3A4 inhibitor (e.g. erythromycin) on the pharmacokinetics of bosutinib. The proposed protocol must be submitted for review and concurrence prior to trial initiation.
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PMR/PMC Schedule Milestones:

Final protocol Submission Date: 03/17/2013

Study/Clinical trial Completion Date: 09/17/2014

Final Report Submission Date: 03/17/2015

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/s/  
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DIANE C HANNER  
08/07/2012



NDA 203341

Ms. Elizabeth Paige Brown Strong

(b) (6)

Dear Ms. Brown:

Thank you for agreeing to provide your assistance in the review of the New Drug Application for Bosutinib. Please find the enclosed Briefing Package for your review. A written response to the question posed in the document is requested by August 06, 2012, if possible.

The information enclosed is strictly confidential and should not be shared with anyone.

Please contact Ms. Virginia Kwitkowski (Clinical Team Leader, Division of Hematology Products) for any questions or clarifications regarding the Briefing Document.

Her contact information is: Phone: (301) 796-2318; Email: [Virginia.kwitkowski@fda.hhs.gov](mailto:Virginia.kwitkowski@fda.hhs.gov)

Sincerely,

*{See appended electronic signature page}*

CDR Diane Hanner  
Senior Program Management Officer  
Division of Hematology Products  
Office of Hematology and Oncology Drug  
Products  
Center for Drug Evaluation and Research

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/s/  
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DIANE C HANNER  
08/01/2012

## Executive CAC

**Date of Meeting: July 17, 2012**

**Committee:** David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Haleh Saber, Ph.D., DHOT, Supervisor and Alternate Member  
Shawna Weis, Ph.D., DHOT, Presenting Reviewer

### **Author of Draft:**

Shawna Weis

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

NDA #203341

Drug Name: Bosutinib

Sponsor: Wyeth (Pfizer)

### **Background:**

Bosutinib is an Abl and Src kinase inhibitor that is undergoing development for Ph(+) CML in adult patients with resistance or intolerance to prior therapy. Bosutinib was negative in the Ames and *in vitro* chromosome aberration assays, both with and without activation by Arochlor-induced S9 extracts. Bosutinib was also negative in the *in vivo* micronucleus assay in rats. A protocol (SPA) and supporting toxicity data were submitted to the CAC for the 2-year rat study in June of 2009, and concurrence was obtained on dose selection for this study. All males were terminated during Week 91 due to excessive mortality. Females were terminated during Week 100.

### **Rat Carcinogenicity Study**

Sprague-Dawley rats were dosed daily by oral gavage in a 10 mL/kg dose volume. Doses were 0 (water), 0 (vehicle), 0 (vehicle), 1.5, 5, and 15 mg/kg/day for females and 0 (water), 0 (vehicle), 0 (vehicle), 2.5, 7.5, and 25/15 mg/kg/day for males. Due to the large number of deaths, doses were reduced for males in the high dose cohort during Study Week 78, and then suspended during Study Week 79 until termination in Study Week 86.

Each dose group consisted of 60 males and 60 females, plus an appropriate number of toxicokinetic satellite cohorts to permit confirmation of exposure and toxicokinetic assessment on Study Day 182. Doses were administered by gavage in a vehicle suspension (0.5% carboxymethylcellulose 2% polysorbate 80, and 0.06% glacial acetic acid). Three control groups, (two vehicle and one water group), were employed in this study.

This study was relocated from the Sponsor facility in Chazy, NY to the CRO site in (b) (4)

during week 36 of dosing.

Plasma exposure levels achieved in this study were up to 1.5-3-fold (AUC $\tau$ ) greater than those anticipated clinically at the 500 mg/day dose level.

**Executive CAC Recommendations and Conclusions (Rat):**

- The Committee agreed that the study was acceptable, but noted that moving an ongoing carcinogenicity study is undesirable and rendered historical control data difficult to interpret due to numerous differences between the two sites.
- The Committee concurred that the study was negative for drug-induced neoplasms.

David Jacobson-Kram, Ph.D.

Chair, Executive CAC

cc:\

/Division File, NDA 203341; DHP

/Haleh Saber; DHOT

/Shawna Weis, DHOT

/Diane Hanner, CSO/PM, DHP

/Adele Seifried, OND IO

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/s/

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ADELE S SEIFRIED  
07/18/2012

DAVID JACOBSON KRAM  
07/18/2012



NDA 203341

## INFORMATION REQUEST

Wyeth Pharmaceutical, Inc  
Attention: Carl M DeJuliis, Pharm D  
Director, Worldwide Regulatory Strategy  
445 Eastern Point Road, MS-8260-1123,  
Groton, CT 06340

Dear Dr. DeJuliis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bosulif (Bosutinib) Tablets.

We also refer to the Agency's Information Request dated March 23, 2012 and your response dated April 5, 2012.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following additional comments and information requests. We request a written response by July 19, 2012 in order to continue our evaluation of your NDA.

We have reviewed the referenced material and have the following comments and requests for information.

### **Revise the post-approval stability commitment in Section P.8.2 as follows:**

- Perform stability studies using the same stability protocol as that used in the NDA submission at long-term conditions (25°C/60%RH) covering at least the granted shelf-life period and at accelerated conditions (40°C/75% RH) up to 6 months for the first three production batches of bosutinib 100 mg and 500 mg strength tablets to be packaged in the intended commercial container closure system.
- Submit the above stability data using the appropriate regulatory mechanism when available.
- Alternatively, designate the commercial container closure system as the container closure system used in the primary stability study program. You may request a post-approval change for the new container closure system via a CMC supplement when sufficient stability data in the new container closure system becomes available to support a marketed shelf life.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

*{See appended electronic signature page}*

Sarah C. Pope Miksinski, Ph.D.  
Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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JANICE T BROWN

07/18/2012

Janice Brown for Sarah Pope Miksinski, Ph.D.

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Tuesday, July 10, 2012 9:41 AM  
**To:** 'Dejuliis, Carl M'  
**Subject:** NDA 203341 Bosutinib Container labeling comments  
**Importance:** High

Hi Carl,

Please note the container labeling comments below regarding NDA 203341 (Bosutinib):

A. Container Labels (100 mg and 500 mg trade bottle)

1. Unbold the dosage form "tablets". Additionally, ensure the established name (which consists of the active ingredient plus the dosage form) has prominence commensurate with the prominence of the proprietary name, including typography (size, font, etc.), layout, contrast, and other printing features, as per 21 CFR 201.10(g)(2).
2. Add the statement "Do not crush or cut tablet" on the front principal display panel.
3. Add the statement "For Oncology Use Only" on the front principal display panel.
4. Change the wording on the Storage condition statement to read "Store at 20°C to 25°C (68°F to 77°F); excursions..." rather than "Store at 25°C (77°F); excursions..."
5. Ensure that the expiration date and lot number is printed on each container label, as per 21 CFR 201.17 and 21 CFR 201.18. It is unclear from the label images submitted whether there is a placeholder for this information.
6. Revise "MADE IN SPAIN" to

(b) (4)

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
07/10/2012

## Newman, Tyree

---

**From:** Newman, Tyree  
**Sent:** Friday, July 06, 2012 11:26 AM  
**To:** 'carl.m.dejuliis@pfizer.com'  
**Cc:** Hanner, Diane  
**Subject:** NDA 203341 - Information request

Good morning Dr. DeJuliis, regarding NDA 203341, please provide a response to the following information request by the **close of business on July 10, 2012**, to the attention of Diane Hanner:

**Please send the narratives for two additional subjects who died within 30 days of treatment with bosutinib: Patient 002793 and Patient 002798. Also, please send information about the patient with breast cancer in a trial of bosutinib and letrozole who had a concurrent elevation in ALT a > 3 X ULN and total bilirubin > 2 X ULN without elevated alkaline phosphatase < 2 X ULN.**

Kind regards,

Tyree

Tyree Newman  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
301-796-3907 (phone)  
301-796-9845 (fax)  
Tyree.Newman@fda.hhs.gov

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/s/  
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TYREE L NEWMAN  
07/06/2012

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Friday, June 08, 2012 9:33 AM  
**To:** 'Dejuliis, Carl M'  
**Subject:** NDA 203341 Bosutinib- CML Disease Phase Definition

**Follow Up Flag:** Follow up  
**Flag Status:** Red

Hi,  
Please provide the source for the Tables Defining Disease Phases and Responses to Treatment (Attachment 1 on page 47 of the Statistical Analysis Plan).  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
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E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
06/11/2012

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** May 24, 2012  
**TIME:** 10:30PM- 11:00PM (EST)  
**LOCATION:** TCON/CDER WO 1415  
**APPLICATION:** NDA 203341 (QbD Supplement)  
**DRUG NAME:** Bosulif  
**TYPE OF MEETING:** FDA initiated TCON  
**MEETING CHAIR:** Janice Brown, CMC Team Lead  
**MEETING RECORDER:** Jewell Martin, Regulatory Health Project Manager  
**MEETING PURPOSE:** The purpose of the TCON was to discuss the Agency's Information Request dated May 3, 2012 and applicant's response dated May 16, 2012.

### **FDA Attendees:**

Janice Brown, MS, ONDQA Lead  
Joyce Crich, PhD, ONDQA Reviewer  
Debasis Ghosh, PhD, ONDQA Reviewer  
Vipul Dholakia, PhD, OMPQ Compliance Officer  
Jewell Martin, MA, MBA, PMP, ONDQA Regulatory Health Project Manager

### **Pfizer Attendees:**

Susan Decoteau, Principal Scientist, GCMC  
Steven Guinness, Principal Scientist, CRD  
Frank Busch, PhD, Research Fellow, CRD  
Karen Sutherland, PhD, Director, CRD  
Kevin Girard, PhD, Associate Research Fellow, CRD  
Karen Bronk, PhD, Associate Research Fellow, ARD  
Kyle Leeman, Sr. Principal Scientist, ARD  
Kathleen Zandi, PhD, Associate Research Fellow, Pharm Sciences Team Leader  
Susan Berlam, MS, R.PH, Director GCMC  
Carl DeJuliis, Pharm D, Director, WRS  
Albert Kraus, PhD, Senior Director, WRS  
Nathalie Bouxin, PhD, Asset Team Lead

### **Discussion:**

Minutes are based on CMC discussion in response to the applicant's submission dated May 16, 2012 to an Information Request Letter dated May 3, 2012. On May 23, 2012 FDA sent a written response to applicant's May 16, 2012 response. For convenience those responses are listed in black font. Agreements reached at the teleconference follow in red font.

Query 1(a): Acceptable. In the amendment, submit spike/purge data and batch data for PGIs in S.4.5 or appropriate sections of S.2.

- The applicant acknowledged FDA's response and will submit spike/purge data for potential genotoxic impurities in S.2.

Query 1(b): Acceptable. In the amendment, submit spike/purge data for (b) (4) in the appropriate section to justify that no in-process testing for (b) (4) is needed.

- The applicant acknowledged FDA's response.

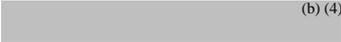
Query 2: Unacceptable. Following process parameters ranges for the manufacturing of drug substance are not supported by adequate data.

Revise the operating ranges for the following process parameters in the description of the process or justify the open or wide ranges with DoE, multivariate PAR, detailed experimental data, in-process control strategies, and similar information:

- The Agency explained that a stand alone document should be provided that can be used for manufacturing of the drug substance. Each step should have an in process control which is currently not included in the manufacturing description.
- The Agency requested process parameter target values/current normal operating ranges be specified in section 3.2.S.2.2.

(b) (4)



Query 3: Confirm the standard deviation for the volumetric  (b) (4)

(b) (4) method 1a for the measurement of (b) (4) content in API, bosutinib monohydrate.

- The applicant acknowledged FDA's response and will provide data for the standard deviation of the test to support the proposed acceptance criterion for (b) (4) in an amendment.

Query 4: Acceptable.

Query 5: Acceptable. In the amendment provide a justification that the API does not convert to impurities (b) (4) during storage.

- The applicant acknowledged FDA's response and will provide a justification in an amendment.

Query 6: Acceptable.

Query 7: Acceptable.

Query 8: Acceptable.

- The applicant made a commitment to provide data by May 31 and to submit updated responses including the eCTD sections.

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/s/  
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JEWELL D MARTIN  
06/25/2012

JANICE T BROWN  
06/26/2012



NDA 203341

**GENERAL ADVICE**

Wyeth Pharmaceutical, Inc  
Attention: Carl M DeJuliis, Pharm D  
Director, Worldwide Regulatory Strategy  
445 Eastern Point Road, MS-8260-1123,  
Groton, CT 06340

Dear Dr. DeJuliis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bosulif (Bosutinib) Tablets.

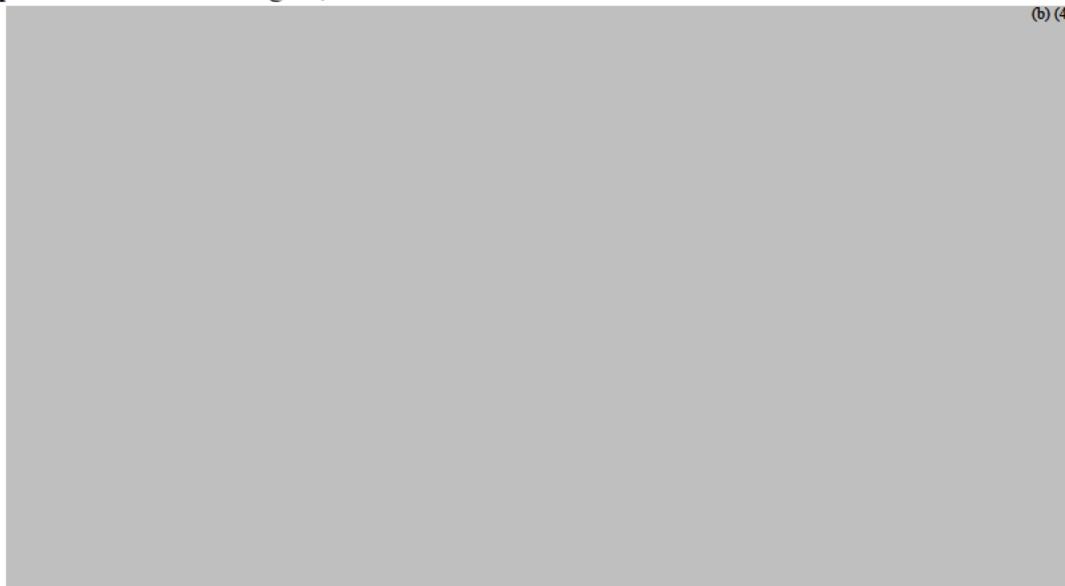
We also refer to the Agency's Information Request dated May 3, 2012 and your response dated May 16, 2012.

Query 1(a): Acceptable. In the amendment, submit spike/purge data and batch data for PGIs in S.4.5 or appropriate sections of S.2.

Query 1(b): Acceptable. In the amendment, submit spike/purge data for (b) (4) (b) (4) in the appropriate section to justify that no in-process testing for (b) (4) (b) (4) is needed.

Query 2: Unacceptable. Following process parameters ranges for the manufacturing of drug substance are not supported by adequate data.

Revise the operating ranges for the following process parameters in the description of the process or justify the open or wide ranges with DoE, multivariate PAR, detailed experimental data, in-process control strategies, and similar information:





(b) (4)

Query 3: Confirm the standard deviation for the volumetric method 1a for the measurement of <sup>(b) (4)</sup> in API, bosutinib monohydrate.

Query 4: Acceptable.

Query 5: Acceptable. In the amendment provide a justification that the API does not convert to impurities <sup>(b) (4)</sup> during storage.

Query 6: Acceptable.

Query 7: Acceptable.

Query 8: Acceptable.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

*{See appended electronic signature page}*

Janice Brown, MS  
CMC Team Lead, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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JANICE T BROWN  
05/23/2012



NDA 203341

**INFORMATION REQUEST**

Wyeth Pharmaceutical, Inc  
Attention: Carl M DeJuliis, Pharm D  
Director, Worldwide Regulatory Strategy  
445 Eastern Point Road, MS-8260-1123,  
Groton, CT 06340

Dear Dr. DeJuliis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bosulif (Bosutinib) Tablets.

We also refer to the Agency's Information Request dated March 23, 2012 and your response dated April 5, 2012.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following additional comments and information requests. We request a written response by May 16, 2012 in order to continue our evaluation of your NDA.

We have reviewed the referenced material and have the following comments and requests for information.

**Drug Substance**

1. In addition to the provided in-process controls (b)(4) in your response of 05-Apr-2012, implement and provide the following in-process controls as the alternatives for the related tests are not included in the proposed drug substance specifications.
  - a. Tests with appropriate acceptance limits for potential genotoxic impurities at appropriate step(s)
  - b. Tests for (b)(4) with appropriate acceptance limits at end (b)(4) or other appropriate step.
2. Your revised manufacturing process description in 3.2.S.2.2 submitted in amendment of the 05-Apr-2012 amendment only addressed some of the items as requested in the Agency's 23-Mar-2012 Information Request Letter. Refer to Query No. 2 and No. 3 in the Agency's Information Request Letter of 23-Mar-2012.

In order to provide a complete description of the commercial scale drug substance manufacturing processes that includes all the revised process parameters and applicable

set points or ranges, include information for the following in Section 3.2.S.2.2, with appropriate justification in Section 3.2.S.2.6 to support the proposed ranges/set points.



3. Tighten the proposed acceptance criterion for (b) (4) in the drug substance specifications, as it is much wider than the theoretically possible amount of (b) (4) for bosutinib monohydrate, and is also greater than the actual (b) (4) in manufactured drug substance batches. Alternatively, provide justification for the proposed acceptance criterion for (b) (4) including the possibility of hydrates other than the monohydrate when (b) (4) differs from (b) (4) such as (b) (4). Provide supporting data to confirm the API is in monohydrate form when (b) (4).
4. Include a polymorphic identification test in the proposed drug substance specification.
5. Test and report organic impurities (specified, individual unspecified and total organic impurities) in the post-approval stability protocol according to the proposed drug substance specifications. Provide justification for the impurity testing report in the stability studies which only covers “Total Organic Impurities” and “Largest Single Unspecified Impurities”, while the three specified organic impurities (b) (4) are not listed (e.g. relationship between API and these three impurities during storage). Confirm that “Total Organic Impurities” in the stability studies includes these impurities.

### Drug Product

6. Provide in-process control specifications including a proposed test method and acceptance criterion for content uniformity (weight variation) of bosutinib uncoated

tablets, if the content uniformity test is not included in the proposed regulatory specification for drug product.

7. Include the following tests in the proposed regulatory specification for drug product (refer to ICH Q6A)
  - a. Degradation product (both individual and total) testing at release and on stability
  - b. (b) (4) testing at release and on stability
  
8. Your manufacturing process description in section P.3.3 is inadequate and does not provide a complete understanding of the drug product manufacturing process and in-process controls. Adequate information should be provided to describe all the manufacturing steps and in-process controls, including the non critical process parameters. Thus, in accordance with 21CFR 314.50(d)(ii)(c), either 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) OR provide a process description to section P.3.3 that is comparably detailed to the master batch record.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

*{See appended electronic signature page}*

Sarah C. Pope Miksinski, Ph.D.  
Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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SARAH P MIKSINSKI  
05/03/2012

**Hanner, Diane**


---

**From:** Hanner, Diane  
**Sent:** Wednesday, April 18, 2012 12:01 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** NDA 203341 (Bosutinib) Request and Submission Updates  
**Importance:** High

Hi ,

I need to alert you that you should update the NDA 203341 (Bosutinib) with the micro testing laboratory **asap**, preferable before 5 weeks since in the unlikely event, the site may need to be reinspected.

Regards,  
Diane

---

**From:** Dejuliis, Carl M [mailto:carl.m.dejuliis@pfizer.com]  
**Sent:** Wednesday, April 04, 2012 4:57 PM  
**To:** Hanner, Diane  
**Subject:** NDA Request and Submission Updates

Hi Diane,

As discussed, here is a status update on the outstanding requests:

1. It appears that the (b) (4) company has received a warning letter. It also appears that this public knowledge, and it showed up during the review of NDA 203341 (Bosutinib). (Notification dated 3/28/12)

*In the Bosutinib NDA, (b) (4) is listed as our microbiological testing site. We plan to amend the NDA in order to replace the (b) (4) testing site for mico testing with our (b) (4) (Pfizer) (b) (4) for the microbiological testing of Bosutinib. Currently, (b) (4) is listed in the Bosutinib NDA as a packaging, labeling, testing and release site. We are currently validating this site and our plan is to amend the NDA after we complete the validation (approximately 5 weeks). Axitinib (NDA 202324) uses the (b) (4) site for its micro testing.*

*Is this plan acceptable to you?*

2. CMC Information Request (dated 3/23/12, received 3/27/12)

*The responses to these queries will be submitted, as requested, on April 6<sup>th</sup>. I will let you know when they are transmitted.*

3. Request for the 120-DAY Safety Update Datasets (request dated 3/28/12)

*These datasets will be transmitted either tomorrow or Friday. They are going through a final submission QC. I will let you know when they are sent out.*

4. The request for the application to contain narratives for all SAEs or deaths (requested dated 3/28/12)

*Originally, it was agreed that we would only submit narratives for related SAEs. Therefore, we will need a little time to prepare the narratives for the unrelated. We have started work on these. Our plan is to submit the unrelated SAEs for studies 200 and 3000. We should have them submitted within a couple weeks.*

*Is this acceptable to you?*

5. Update Financial Disclosure Information

*This information should be submitted next week.*

FYI: Next week (Tuesday thru Friday), I will be in New York preparing for a potential Bosutinib ODAC (our second MOCK), so if you need to get in touch with me please use email or call me on my cell phone, and I will get back to as soon as possible.

If you have any questions, please let me know.

Thank You and Best regards,

Carl DeJuliis

Pfizer, Inc  
MS 8260-1123  
445 Eastern Point Road  
Groton, Ct 06340  
Office Phone: 860-441-1693

(b) (6)

[carl.m.dejuliis@pfizer.com](mailto:carl.m.dejuliis@pfizer.com)

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/s/  
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DIANE C HANNER  
04/18/2012

**From:** [Hanner, Diane](#)  
**To:** ["Dejuliis, Carl M"](#)  
**Bcc:** [Mello, Robert](#); [McGinn, Karen](#); [Kwitkowski, Virginia](#)  
**Subject:** Information request for NDA 203341 Bosulif  
**Date:** Monday, April 16, 2012 1:26:47 PM

---

Hi,

I have been instructed to convey the following regarding NDA 203341 (Bosutinib):

Your proposal to [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4) you

may propose to omit finished product microbial limits testing for batch release and substitute in-process manufacturing controls, tests and acceptance criteria that provide assurance of the microbiological quality for each batch of your product. Such process controls, tests and acceptance criteria should be identified as part of the manufacturing process controls for inclusion in the batch record and should include, for example:

- Microbial limits data for critical raw materials
- Microbiological environmental monitoring data for critical processing steps that can be related to the batch, and
- In-process control parameters (e.g., heat, drying, washing) that may affect product quality microbiology.

Also, in addition to continuing the microbial limits testing on the current registration batches within the initial stability program, microbial limits testing should be performed at the initial time point, T=0 (at a minimum) for those commercial lots placed into the post-approval, long term stability program.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
04/16/2012

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Wednesday, March 28, 2012 2:45 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** Information request regarding NDA 203341 (Bosutinib)  
**Importance:** High

Hi,  
Please address the following information request regarding Bosutinib:  
Your recent 120-day Safety Update did not include the datasets. The datasets are required for analysis by the Agency. In addition, the application should include narratives for all SAEs or deaths.

Thank you.

Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
03/28/2012



NDA 203341

**INFORMATION REQUEST**

Wyeth Pharmaceutical, Inc  
Attention: Carl M DeJuliis, Pharm D  
Director, Worldwide Regulatory Strategy  
445 Eastern Point Road, MS-8260-1123,  
Groton, CT 06340

Dear Dr. DeJuliis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bosulif (Bosutinib) Tablets.

We also refer to your November 17, 2011 original NDA submission.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by April 6, 2012 in order to continue our evaluation of your NDA.

**Drug Substance**

1. Establish an in process control strategy and provide a detailed description of the test methods and acceptance criteria for the relevant manufacturing steps.
2. The proposed approach to control the drug substance manufacturing process within the Proven Acceptable Range (PAR) values is not adequately supported by the data provided in your submission. However, the Target Value/Normal Operating Ranges (NOR) appear to be reasonable and may be included in the process description. Revise the drug substance manufacturing process description to reflect the above changes. Alternatively, justify the proposed PAR with adequate supporting data.
3. Your application must include a full description of the drug substance including the method (b) (4) of the drug substance and the process controls used during manufacture and packaging. Your current manufacturing process description is not adequate. Provide a complete description of the commercial scale drug substance manufacturing processes that includes all process parameters and applicable set points or ranges. Include the detailed manufacturing process description in Section 3.2.S.2.2 (drug substance).

(b) (4)

4. [REDACTED] (b) (4) include a test for polymorphic identification in the proposed drug substance specification. Furthermore, indicate if there is any potential for polymorphic conversion during the course of drug product manufacture and shelf life. If yes, clarify your approach to control and monitor such changes. In addition, provide solubility profiles for the drug substance polymorphic forms [REDACTED] (b) (4) to describe their impact on dissolution.
5. Include [REDACTED] (b) (4) testing in the proposed drug substance specification.
6. Provide data to justify that th [REDACTED] (b) (4) It is noted that the drug substance batches used (08-044, RB7633 & 08-002) for the study of particle size effect on dissolution had a three-tier measurement and the highest value for the [REDACTED] (b) (4) [REDACTED] (b) (4) Therefore, either tighten the proposed particle size limit appropriately or provide additional dissolution data to justify the proposed limit.
7. Clarify whether the acceptance criteria for “individual unspecified impurities NMT [REDACTED] (b) (4) applies to potential genotoxic impurities (PGIs).
- Alternatively, provide supporting data to justify the omission of PGIs testing in the drug substance specifications, including a detailed description of in-process controls for PGIs and detection limits for PGIs.
8. Tighten the proposed drug substance acceptance criterion for “Total Organic

Impurities. NMT (b) (4) as it is greater than the sum of the proposed acceptance limits for individual specified and unspecified impurities in the drug substance specifications and is substantially higher than the actual levels noted in the clinical lots of drug substance.

9. Provide supporting data and a detailed description of in-process controls for (b) (4) (b) (4) to justify the omission of (b) (4) testing in the proposed drug substance specifications.
10. In your stability protocol, the proposed annual testing frequency for long term storage conditions does not conform with recommendations in ICH Q1A(R2). Revise the proposed stability protocol accordingly.

### **Drug Product**

11. Submit updated long term and accelerated stability data for bosutinib drug product batches in the proposed commercial container closure system.
12. Provide supporting data addressing the impact of the amount of (b) (4) in the container closure system on the drug product stability. Confirm the potential effect of factors other than MVTR, (eg., dessicant, canisters, headspace, etc.) on drug product stability in the proposed commercial container closure.
13. In the proposed post approval stability protocol for shelf life confirmation and annual lots (refer Tables 3.2.P.8.2.(1 and 2)), revise the sampling points for the first year to every three months, every six months for the second year, and every twelve months thereafter for the long term conditions, as recommended in ICH Q1 A(R2).

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072

Sincerely,

*{See appended electronic signature page}*

Sarah C. Pope Miksinski, Ph.D.  
Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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SARAH P MIKSINSKI  
03/23/2012

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Friday, March 02, 2012 2:20 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** NDA 203341-Bosutinib-Information Request

Hi,

I was instructed to request that the following information regarding Bosutinib (NDA 203341) be sent in within 10 business days from today.

"Please submit the population PK analysis dataset for study PMAR-219 titled "Data8 \_edited\_final\_cov\_log4.csv" as an .xpt file. Also submit the ".R" code that will generate population PK analysis dataset "Data8\_edited\_final\_cov\_log4.csv", relevant to study PMAR-219. The code you provided ("subset-pkdata-r.pdf") produces "Data7\_edited\_final\_cov\_log4.csv" and does not indicate exact changes between the two datasets.

Thanks.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
03/02/2012

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Thursday, February 16, 2012 5:36 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** FW: NDA 203341 bosutinib Information Request

Hi,

I have been instructed to sent you the following Information Request regarding NDA 203341 (IND 068268) bosutinib. Please provide the following individual patient line listings, by clinical site, for U.S. studies conducted by Dr. Cortes (Site #001) and Dr. Khoury (Site #017) only: (1) concomitant and prohibited medications, and (2) efficacy endpoints from bone marrow, peripheral blood and physical examinations.

For the efficacy endpoints, please include per patient data on the following:

- (i) Hematologic responses to treatment in terms of specific bone marrow and peripheral blood findings. For example, please submit specific patient data listings for bone marrow blast and basophil percentage findings, platelet count, total white blood cells, absolute neutrophil count, peripheral blood basophils, and/or other significant findings such as promyelocytes, and
- (ii) Presence or absence of extramedullary (e.g., spleen, lymph node or liver) involvement for CML patients, e.g., patient physical examination results during their clinical trial visits.

Please submit information requested by February 21, 2012.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
02/16/2012



NDA 203341

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Wyeth Pharmaceutical, Inc.  
445 Eastern Point Road  
MS-8260-1123  
Groton, Connecticut 06340

ATTENTION: Carl M. Dejuliis, Pharm.D.  
Director, Worldwide Regulatory Strategy

Dear Dr. Dejuliis:

Please refer to your New Drug Application (NDA) dated November 17, 2011, received November 17, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bosutinib Monohydrate Tablets, 100 mg and 500 mg.

We also refer to your November 17, 2011, correspondence, received November 17, 2011, requesting review of your proposed proprietary name, Bosulif. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Bosulif, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your November 17, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Diane Hanner at (301) 796-4058.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
02/07/2012



NDA 203341

**METHODS VALIDATION  
MATERIALS RECEIVED**

Wyeth Pharmaceuticals, Inc.  
Attention: Carl DeJuliis, Pharm.D.  
500 Arcola Road  
Collegeville, PA 19426-3982

Dear Carl DeJuliis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bosulif (bosutinib monohydrate) tablets and to our 12/22/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 1/26/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
01/27/2012



NDA 203341

**FILING COMMUNICATION**

Wyeth Pharmaceuticals, Inc.  
Attention: Carl M. DeJuliis, Pharm. D  
Director, Global Regulatory Affairs  
445 Eastern Point Road  
Groton, CT 06340

Dear Dr. DeJuliis:

Please refer to your New Drug Application (NDA) dated November 17, 2011, received November 17, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for bosutinib monohydrate, 100 mg and 500 mg oral Tablets.

We also refer to your amendments dated December 20, 2011; December 22, 2011(3); December 23, 2011; and January 04, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 17, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 30, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Provide the specific details for the development of the dissolution method (ref section 2.3.P.2) along with the complete dissolution data collected during this development.

2. Provide the multi time-point dissolution data for all the batches used in the PK and clinical studies listed in table 1, under section: 2.3.P.2, which are needed to evaluate the acceptability of your proposed dissolution acceptance criterion.
3. Please provide a release specification for microbial limits of the drug product or provide an acceptable justification, which would include appropriate supportive data, for not having such a microbial limit specification.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, M.D.  
Director (acting)  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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ANN T FARRELL  
01/26/2012

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Friday, December 23, 2011 11:39 AM  
**To:** 'Dejuliis, Carl M'  
**Subject:** IR for NDA 203341 (Bosutinib) regarding MeDDRA coding and CRFs

**Importance:** High

Hi,

I have been instructed to request that you please send the following items that are required for the clinical review regarding NDA 203341 (Bosutinib):

1. MeDDRA coding dictionary with a list of all investigator verbatim terms and the preferred terms to which they were mapped;
2. CRFs for all SAEs regardless of attribution. Since Trial 200 was a single arm trial, attributions cannot be made except for adverse events that are clearly not related, e.g, automobile accident, or are progression events.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
12/23/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Thursday, December 22, 2011 2:11 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** Bosutinib - NDA 203341

Hi,

I have been instructed to convey that according to our data-manager are still in need of the following regarding NDA 203341 (Bosutinib):

Please update datasets ECGTES.XPT, ECGAV.XPT with values of QTcl correction factor (slope) for each subject, values of QTcl and values of QTcN added.

Thank you.  
Regards,  
Diane

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**From:** Dejuliis, Carl M [mailto:carl.m.dejuliis@pfizer.com]  
**Sent:** Tuesday, December 20, 2011 2:08 PM  
**To:** Hanner, Diane  
**Subject:** FW: Bosutinib FDA (ECG/DEMOG) Response 0001 Submitted - NDA 203341

Hi Diane,

Your request for the ECG datasets and information for study 105 was dispatched today. Attached is the cover letter, the 365h form and the acknowledgement.

Regards,

Carl

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/s/  
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DIANE C HANNER  
12/22/2011



NDA 203341

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Wyeth Pharmaceuticals Inc.  
Attention: Carl DeJuliis, Pharm.D.  
500 Arcola Road  
Collegeville, PA 19426-3982

Dear Carl DeJuliis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bosulif (bosutinib monohydrate) tablets, 100 mg and 500 mg.

We will be performing methods validation studies on Bosulif (bosutinib monohydrate) tablets, 100 mg, as described in NDA 203341

In order to perform the necessary testing, we request the following sample materials and equipments:

60 Tablets Bosulif (bosutinib monohydrate) tablets, 100 mg  
100 mg Bosutinib Drug Substance  
300 mg Bosutinib Monohydrate Reference Standard  
25 mg PF-05342710 Reference Material  
25 mg PF-05891450 Reference Material  
25 mg PF-05343292 Reference Material  
25 mg PF-05312061 Reference Material  
25 mg PF-05343643 Reference Material  
25 mg PF-05343634 Reference Material  
25 mg PF-05321066 Reference Material  
1 Waters Sunfire, C18, 150 mm x 4.6 mm, 3.5  $\mu$ m

Please include the MSDSs and certificates of analysis for the samples and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: James F. Allgire  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
12/22/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Thursday, December 15, 2011 3:19 PM  
**To:** 'Dejuliis, Carl M'  
**Subject:** NDA Bosutinib 203341-IR 12-15-11  
**Importance:** High

Hi,

I have been instructed to convey the following regarding NDA 203341 (bosutinib):

**We have requested a tcon with you to discuss several problems with your submission which present filing issues. You have submitted datasets in series of twos, threes and fours with the same names but collected at different time points. For example, Study-200 data tabulation datasets (5.3.5.25.1.1) lists datasets in triplicate (e.g., death, demole) and dataset sizes are different even if listed with the same name. This problem is noted with Study-3000 data tabulation and analysis datasets as well. The Division of Hematology Products prefers to see and review the most current data.**

**If there is ever the need to have data from multiple cut-off dates, it is recommended that each cutoff date be provided in a separate submission sequence so that proper lifecycle (new, append, delete, and replace) is used on documents and files. This approach would allow only the current versions to be displayed. Please also confirm that the most recent datasets will include all of the data from the prior earlier datasets.**

**Since there is no need for older data in this application, you should perform steps 1 and 2 below to fix the application.**

- 1. Submit a new submission sequence.**
- 2. Use the eCTD lifecycle operator attributes (new, append, delete, and replace) to fix the submission so that only the most current data for each study including the SCS are showing as the current versions. Additionally, the SCS define.pdf file tags need to be corrected. Two data definition files were tagged as data-tabulation-dataset, but should be tagged as data-tabulation-data-definition.**

**Additional Comment: Please note that this is not a comprehensive list of all the issues with NDA 203341 and it only reflects the issues that we investigated as a result of a reviewability issues with data. In the future, detailed information about the submission including multiple cut off dates, leaf titles, placement of information, etc. should be discussed at the PreNDA or an electronic submission meeting with the sponsor/applicant so that this type of issue can be avoided.**

Thank you.

Regards,

Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OHOP/DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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DIANE C HANNER  
12/15/2011

**From:** [Hanner, Diane](#)  
**To:** ["Dejuliis, Carl M"](#)  
**Bcc:** [Kozeli, Devi](#); [Kwitkowski, Virginia](#); [McGinn, Karen](#); [De Claro, R. Angelo](#); [Pfuma, Elimika](#); [Bullock, Julie](#)  
**Subject:** Information request (12-12-11) regarding - NDA 203341 (Bosutinib)  
**Date:** Monday, December 12, 2011 3:52:00 PM  
**Importance:** High

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Hi,

I have been instructed to request the following information regarding NDA 203341 (Bosutinib):

1. DEMOG dataset with basic information such as subject ID, age, race, ethnic, sex, weight, height, bmi and etc..
2. ECG analysis dataset (average of triplicate ECGs) with basic information such as part, period, sequence, treatment, nominal day, nominal time, QTcl correction factor for each subject and etc..
3. ECG raw dataset in triplicates with date, time (up to second) and other basic information, please provide a mapping file if ECG dataset subject IDs are different from warehouse subject IDs.

Thank you.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/ DHP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
12/12/2011



NDA 203341

**NDA ACKNOWLEDGMENT**

Wyeth Pharmaceuticals, Inc.  
Attention: Carl M. DeJuliis, Pharm. D  
Director, Global Regulatory Affairs  
500 Arcola Road  
Collegeville, PA 19426-3982

Dear Dr. DeJuliis:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (Bosutinib monohydrate 100 mg and 500 mg oral tablets)

Date of Application: November 17, 2011

Date of Receipt: November 17, 2011

Our Reference Number: NDA 203341

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 16, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me, at (301) 796-4058.

Sincerely,

*{See appended electronic signature page}*

CDR Diane Hanner  
Senior Program Management Officer  
Division of Hematology Products  
Office of Hematology and Oncology Drug  
Products  
Center for Drug Evaluation and Research

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DIANE C HANNER  
11/22/2011

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 23, 2007  
**TIME:** 12:00 Noon  
**LOCATION:** Teleconference  
**APPLICATION:** IND 68,268  
**DRUG NAME:** Bosutinib (SKI-606)  
**TYPE OF MEETING:** Type B, MR # 150, MP# 158

**MEETING CHAIR:** John Johnson, M.D.

**MEETING RECORDER:** Carl Huntley, R. Ph., MBA

### FDA ATTENDEES:

Ann Farrell, M.D., Deputy Division Director, DDOP  
John Johnson, M.D., Medical Team Leader, DDOP  
Bhupinder Mann, M.D., Medical Reviewer, DDOP  
Raji Sridhara, Statistical Team Leader, OTS/OB/DBV  
Jiang (Janet) Xiaoping, Ph. D., Statistical Reviewer, OCP/DCPI  
Carl Huntley, R. Ph., MBA, Project Manager, DDOP

### EXTERNAL CONSTITUENT ATTENDEES:

David Roth, MD, Assistant Vice President, Clinical Research & Development  
Ronald Menton, PhD, Senior Director, Early Development Biostatistics  
Robin Evers, Senior Director, Global Regulatory Affairs  
Becker Hewes, MD, Director, Clinical Research & Development  
Patrick Kelly, MD, Director, Clinical Research & Development  
John D. Alvarez, MD, PhD, , Associate Director, Clinical Translational Medicine, Oncology  
Patricia Martins Harris, MPH, Assistant Director, Clinical Research & Development  
Emily Martin, PhD, Principal Biostatistician, Oncology Biostatistics  
Debra Segal, Manager, Global Regulatory Affairs

(b) (4)

### BACKGROUND:

The IND was submitted on April 16, 2004. An SPA for protocol 316A4-3000-WW was submitted on June 11, 2007 (serial number 131). Responses to this SPA were provided on August 10, 2007. This meeting seeks to clarify issues and reach agreement with the Agency on those responses.

**Proposed Indication:** Bosunitib is being developed for the treatment of adults with Chronic myelogenous leukemia (CML).

## MEETING OBJECTIVES:

The purpose of the meeting is to seek understanding of the Agency's comments on responses to questions originally posed in the SPA of June 11, 2007, with respect to the primary and secondary objectives of the study, the dose escalation criteria and definition of treatment failure, as well as relevant study efficacy endpoints and analyses.

## LIST OF SPECIFIC QUESTIONS, ANSWERS AND DISCUSSION:

**COMMENTS:** Please note that all questions will be included except for questions 8-10 as noted.

Wyeth has requested a Type A Meeting in order to obtain clarification on several of the FDA's responses (1 – 7). No clarification or follow-up are being requested in regard to the Agency's responses to questions 8-10. Wyeth's original questions are in bold font style and the FDA responses are in italic; Wyeth's Responses are provided in regular font style. The Agency responses are such: **Discussion (10/16/07)**. Wyeth's responses are provided in regular, double underlined font: Responses (10/22/07). For purposes of the October 23, 2007 telecommunication, the responses (Discussion 10/23/07) will be single underlined font, non-bolded (questions 1, 2,3,4,7, and discussion (questions 2, 3, and 4).

1. **Does the Agency agree that the endpoint and its method of determination will support accelerated approval in subjects with newly diagnosed chronic phase Philadelphia chromosome positive CML?**

### FDA response:

*We agree with the proposed primary endpoint for accelerated approval: the rate of CCyR at one year, and with the proposed method of determination: standard cytogenetics. (Twenty or more metaphases will be counted for this determination. FISH analysis of bone marrow aspirate or peripheral blood may be used to determine CCyR in the case that cytogenetics are insufficient, i.e. fewer than 20 metaphases). We recommend that there should be a central blinded review of standard cytogenetic and FISH results at baseline and at subsequent assessments.*

### **Wyeth Response**

Wyeth has evaluated the incorporation of centralized assessments, and has determined that logistical and technical obstacles preclude the feasibility of centralized cytogenetic and FISH analyses in a global study. Both conventional cytogenetic and FISH assessments require fresh bone marrow samples. Furthermore, conventional cytogenetic assessments require cell growth in culture for adequate sample preparation and analysis. Shipment of samples to a central or regional reference laboratory could result in a significant loss of useable data and could potentially introduce spurious results due the fragility of the sample specimens. These factors could compromise the ability to adequately and consistently assess therapeutic responses to the test and reference articles.

Wyeth has approached four potential reference laboratories with extensive experience in global trials, and with expertise in sophisticated molecular diagnostic testing procedures. Each time the opinion has been that sample transport and cell growth-related technical issues have resulted in

inconsistencies and have been major issues in previous attempts to perform standardized centralized review in CML trials specifically. To date, for central blinded review of standard testing procedure is available either from Wyeth or a commercial vendor. In addition, Wyeth has discussed this issue with several key opinion leaders, (b) (4) who have expertise in CML; all concur that cytogenetic analysis by the site rather than central review is appropriate.

The design of Wyeth's proposed trial is based on historical data derived from numerous open-label studies, all of which were based upon local cytogenetic response assessment. Moreover, cytogenetic data as assessed by individual sites (as opposed to assessments by a central blinded reviewer) has been used in support FDA review and approval of applications for both imatinib (first line and second line) and dasatinib (second line).

Wyeth acknowledges that central, blinded assessment of treatment effect can minimize potential bias in an open label trial. For this reason, the assessment of the secondary efficacy endpoint, major molecular response (MMR), will be performed by a central vendor. However, Wyeth believes that it is appropriate to use local site assessments of standard cytogenetic and FISH results because of concerns about lack of feasibility of central review and the regulatory precedent for using site-reported data.

**Discussion (10/16/07):**

**FDA understands the steps required in preparing samples for conventional cytogenetics and FISH. Relevant specimens can be prepared locally, the FDA is asking for a blinded review of the prepared material to confirm the findings of the local review.**

**Your proposed study will be comparing your experimental treatment with an active agent in a superiority trial. The proposed study is different than the historical studies you have mentioned and concern with bias is not comparable.**

Wyeth Response (10/22/07)

Wyeth wishes to obtain further clarification on the Agency's recommendation during the teleconference.

Discussion 10/23/07:

FDA proposed as an alternative for Wyeth to conduct a central blinded review of cytogenetics in a proportion of patients to determine concordance between local and centrally recorded information. Wyeth proposed this blinded review would be done at baseline and at a one year interval. FDA agreed to this in principle and would like to see the detailed plan for review. The FDA remains concerned about (b) (4) final response. The FDA emphasized that the local pathologist must be blinded to treatment. If Wyeth is unable to assure the local pathologist blinding, then Wyeth would consider central review of all patients.

2. **Does the Agency agree that the benchmark in the imatinib arm of (b) (4) CCyR rate at 12 months is appropriate and that a (b) (4) improvement is clinically significant?**

FDA response:

*The published rate of CCyR to imatinib at 12 months is 69%, and this rate will be acceptable as the benchmark. Whether an improvement in CCyR to 75% is considered clinically significant will be a review issue and will depend on the risk-benefit assessment.*

*We note that your proposed study (Study 3000) is an open-label study comparing bosutinib and imatinib therapy in patients with newly diagnosed chronic phase CML. We have the following concerns with your proposed study:*

- a. The methods used for response evaluation, the standard cytogenetics and FISH, are operator dependant. We recommend that there be a central blinded review.*
- b. Any imbalances in baseline imatinib resistance mutation status and prior exposure to imatinib between treatment arms will be problematic. We suggest that you consider baseline imatinib resistance mutation status and prior imatinib exposure as randomization stratification factors.*

*Please submit the informed consent form for the proposed study for our review. The data of bosutinib efficacy / activity in CML is limited to the small experience of bosutinib in imatinib resistance CML. It maybe acceptable to conduct a study in the first line setting—with adequate monitoring of the patients; however, the information of the extent of experience with the experimental therapy and the standard therapy must be provided to the patients.*

**Wyeth Response**

Wyeth believes the expected 12 month CCyR rate for imatinib will be approximately 60-65%. Although the published response rate of CCyR to imatinib at 12 months is 69%, this represents an estimated cumulative response rate. The cumulative response rate will be higher because, provided they respond before going off study, even patients who lose their CCyR at month 12, or who discontinue prior to 12 months for disease progression or an adverse event are counted as responders. Wyeth believes that a CCyR rate at 12 months, rather than the cumulative response rate at 12 months, is a more accurate reflection of clinical benefit, and therefore a more appropriate endpoint to benchmark.

This estimate of the expected CCyR for the control arm at 65% was also supported by advice from CML experts. We therefore propose, for the purpose of study design, using 65% as the expected 1-year rate of response in the control arm. Wyeth believes that the study is sufficiently powered to detect a difference of 15% over this benchmark. Please note that the assumption is that 80% of subjects on the bosutinib arm will have a CCyR at 12 months, rather than 75% as cited in FDA comment.

Wyeth understands whether the specific improvement is considered clinically significant will be a review issue and will depend on the risk-benefit assessment.

- a) Response to central blinded review of standard cytogenetic and FISH results:

Please refer to Wyeth's Response to Comment 1, above.

**Discussion (10/16/07):**

**FDA agrees with the control arm (imatinib) estimate of CCyR of 65% at one year and that an absolute increase of 15% (23% improvement over 65%) to a CCyR of 80% may be clinically significant if the risk-benefit ratio is favorable.**

**A cumulative CCyR at one year will be of clinical interest and should be reported as a sensitivity analysis.**

**Wyeth Response (10/22/07)**

**With respect to the cumulative CCyR, Wyeth agrees to add this measure to the sensitivity analyses in the statistical analysis plan (SAP).**

**FDA Discussion 10/23/07: FDA Agrees.**

b) Wyeth does not believe that stratification based on baseline imatinib resistance mutation status is necessary because of the low likelihood that these mutations would be present in newly diagnosed, previously untreated CML patients. While the existence of pre-treatment mutations in accelerated phase, blast phase, and Ph+ ALL patients has been documented, the pre-treatment mutations in these patients have not been reported to correlate with cytogenetic response or other measures of clinical outcome.<sup>1</sup> Wyeth is not aware of any published reports of mutations existing at baseline in early chronic phase CML patients. In addition, the increased time required to sequence a subject's bcr-abl fusion gene during the screening could delay initiation of therapy.

Due to the very limited risk of impact on study outcome as well as concerns regarding potential treatment delays, Wyeth does not plan to stratify based on mutation status at baseline. However, in order to increase our understanding of the treatment associated development of mutations, Wyeth proposes to add pre-treatment and progression-based analysis of mutations to study 3000.

**Discussion (10/16/07):**

**Sponsor responses to b) are acceptable.**

With regard to the request to also use prior imatinib exposure as randomization stratification factor, a maximum of only two weeks of imatinib will be allowed for any study subject enrolled into this trial. In the IRIS trial the median estimated time to Complete Cytogenetic Response (CCyR) was approximately 6 months. The primary efficacy endpoint in the proposed randomized comparative study will be assessed at 12 months. In either instance, a maximum of 2 weeks of prior imatinib therapy is brief relative to the time of anticipated CCyR and assessment of CCyR. It is therefore very unlikely that this degree of imatinib pre-treatment will decrease the disease burden substantially, or influence the estimate of CCyR at 1 year should imbalanced randomization occur by chance. Further, introducing the factor of prior therapy would increase the number of randomization strata from 9 to 18. Wyeth therefore proposes that randomized stratification not include prior imatinib treatment as a third stratification factor. A post-hoc stratified analysis, to include the factor of prior imatinib exposure, will be performed to adjust for potential imbalance in prior therapy in the treatment comparison.

**Discussion (10/16/07):**

**We do not recommend that patients be enrolled on this trial if they have received prior imatinib of any duration.**

Wyeth Response (10/22/07)

Wyeth agrees to exclude patients that have received any prior treatment with imatinib of any duration.

FDA Discussion 10/23/07: FDA Agrees.

A copy of the informed consent form (ICF) for the proposed study is provided as Attachment 2 for your review.

**Discussion (10/16/07):**

**Consent form is acceptable. Please clarify in the consent form the circumstances under which the patient's dose of imatinib may be increased to 600 mg.**

Wyeth Response (10/22/07)

Wyeth agrees to update the consent for to clarify the circumstances under which the patient's dose of imatinib may be increased to 600 mg. Wyeth proposes to add language such as: "Your dose of imatinib or bosutinib may be increased to 600 mg a day if needed. Your dose will be increased by your study doctor if your disease does not seem to be responding adequately to treatment or you lose a previously obtained response to treatment."

FDA Discussion 10/23/07: FDA Agrees.

3. **Does the Agency agree with this strategy to follow all subjects for <sup>(b)</sup><sub>(4)</sub> years, to support conversion of accelerated approval to full approval in subjects with newly-diagnosed chronic phase Philadelphia chromosome positive CML?**

FDA response:

Subjects should be followed up for at least 8 years.

**Wyeth Response**

At the EOP2 meeting held in April 2007, the Agency indicated that <sup>(b)</sup><sub>(4)</sub> years of follow-up could be sufficient. Wyeth seeks to understand the Agency's request for 8 years of follow-up and what specific information is required follow 8 years of follow-up to convert from Accelerated Approval to Full Approval.

**Discussion (10/16/07):**

**As the follow up data available from ongoing studies change, what can be considered adequate follow-up is likely to change. A new agent in a superiority trial has to show improvement over the clinical benefit of the standard treatment, eg, if the standard agent shows overall survival improvement, the new experimental agent must show improvement in overall survival, etc. The FDA is requiring 8 years of follow-up for imatinib.**

Wyeth Response (10/22/07)

Wyeth agrees to 8 years of follow-up.

FDA Discussion 10/23/07: FDA Agrees.

4. **Does the Agency agree with the definition of newly diagnosed chronic phase CML, the allowance for prior exposure to imatinib and the proposed maximum duration of exposure to imatinib?**

FDA response:

We agree with the definition of newly diagnosed chronic phase CML. Please see response to 3 above.

**Discussion (10/16/07):**

**We reiterate that we do not recommend that patients be enrolled on this trial if they have received prior imatinib of any duration.**

Wyeth Response (10/22/07)

As stated under question #2, Wyeth agrees to exclude patients that have received any prior treatment with imatinib of any duration.

FDA Discussion 10/23/07: FDA Agrees.

5. **Does the Agency agree with the dose escalation criteria for the imatinib arm and the decision to take subjects off the study if they require dose escalation to 800 mg?**

FDA response:

The proposed plan for dose escalation is acceptable for the last two criteria listed above. However, the first three criteria need revision. The first criterion should be revised from "Failure to achieve complete hematologic response by month 3" to "Failure to achieve complete hematologic response after 3 months of treatment". The 2nd and the 3rd criteria should be similarly revised.

#### **Wyeth Response**

The first three dose escalation criteria: Failure to achieve CHR by month 3, Failure to achieve Major CyR by month 6, and Failure to achieve Complete CyR by month 12, are based on NCCN and European Leukemia Net Clinical Practice Guidelines. It was the protocol intent that dose escalations for the aforementioned criteria should be based on observations obtained at the month 3, month 6 or month 12 routinely scheduled study visit assessments, respectively. To clarify the intent of the protocol language, Wyeth agrees with the Agency's request to revise the first 3 protocol dose escalation criteria from: by month 3 to after 3 months of treatment, from by month 6 to after 6 months of treatment, and from by month 12 to after 12 months of treatment, respectively.

**Discussion (10/16/07):**

No further discussion

6. **Does the Agency agree with Wyeth's definition of treatment failures?**

FDA response:

See the response to question 5 for the necessary language change.

## Wyeth Response

Wyeth agrees with the Agency's request to revise the wording to from by month N to after month N.

### Discussion (10/16/07):

No further discussion

7. Does the Agency agree with the proposed approach for addressing missing data for
- i) CCyR
  - ii) MMR
  - iii) CHR
  - iv) Time to event responses

### FDA Response:

No. Regarding the proposed approach for addressing missing data, we have the following suggestions:

i) CCyR and ii) MMR: Patients who miss the 48-week visit and have a CCyR at the 36-week and the 72-week visits can be considered responders. All other patients will be considered non-responders.

iii) CHR: In general, using LOCF method to impute missing values is problematic.

iv) Time to event responses: Please provide more details of approach for addressing missing data for the specific time to event response endpoint.

Results of secondary endpoints will generally not be considered for inclusion of efficacy claims unless there is persuasive evidence in analysis of the primary endpoint. The secondary endpoints of which you intend to make claims need to be pre-specified and agreed upon by FDA. In addition, the primary analysis for each of these endpoints needs to be pre-specified and the strong family-wise error rate needs to be properly controlled.

## Wyeth Response

Wyeth agrees with the FDA's recommendation for CCyR and MMR.

Wyeth will not use the Last Observation Carried Forward (LOCF) method to impute any values. For peripheral blood (PB) or bone marrow (BM) differentials that sum to 100%, it will be assumed that there are no missing components. There will be no other method of imputation for PB or BM lab values. Please note that the definition of complete hematologic response (CHR) was inaccurately described in the statistical analysis plan (SAP) and will be revised to be consistent with the definition of CHR in the protocol.

For time to event endpoints, the primary method for handling of missing data method will be censoring. Table 7-1 provides additional detail for censoring for the analysis of the time to event endpoints. A subject withdrawing from the study without experiencing the event of interest will be censored at the last valid (i.e., evaluable) assessment of that event. A subject who dies on treatment, after missing two or more assessments of both hematologic and cytogenetic response,

will be censored for EFS at the last hematologic or cytogenetic assessment. Long-term follow-up will record type and date of progression. A subject who dies after treatment discontinuation during long-term follow-up, after missing two or more long-term follow-up assessments, will be censored for EFS at the last assessment at which the subject was found to be alive. A subject with no baseline assessment will be censored for time to response, time to AP/BP, and EFS at the randomization date.

<b>Table 7-1: Definition of Events, Censoring, and Populations in Time To Event Analyses</b>				
<b>Time to Event Endpoint</b>	<b>Initiating Event</b>	<b>Terminating Event(s) (if multiple terminating events, take earliest)</b>	<b>Censoring Event(s) (if multiple censoring events, take earliest)</b>	<b>Population</b>
Time to CCyR (evaluable population)	First Dose	<ul style="list-style-type: none"> <li>▪ First documented CCyR</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last cytogenetic assessment (if no documented CCyR during follow-up)</li> <li>▪ Progression</li> <li>▪ Death</li> </ul>	Subjects who enter with $\leq$ PCyR, receive a post-baseline cytogenetic assessment, and receive at least one dose of test article
Time to MMR (evaluable population)	First Dose	<ul style="list-style-type: none"> <li>▪ First documented MMR</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last molecular assessment (if no documented MMR during follow-up)</li> <li>▪ Progression</li> <li>▪ Death</li> </ul>	Subjects who enter with $\leq$ PMR, receive a post-baseline molecular assessment, and receive at least one dose of test article
Time to CHR (evaluable population)	First Dose	<ul style="list-style-type: none"> <li>▪ First confirmed CHR</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last hematologic assessment (if no confirmed CHR during follow-up)</li> <li>▪ Progression</li> <li>▪ Death</li> </ul>	Subjects who enter with $\leq$ NEL, receive a post-baseline hematologic assessment, and receive at least one dose of test article
Duration of CCyR (ITT population)	First CCyR on study	<ul style="list-style-type: none"> <li>▪ Loss of CCyR</li> <li>▪ Treatment failure</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last cytogenetic assessment (if no loss of CCyR or treatment failure during follow-up)</li> <li>▪ Death</li> </ul>	Subjects in ITT (all randomized subjects) population that achieve CCyR on Study.
Duration of MMR (ITT population)	First MMR on study	<ul style="list-style-type: none"> <li>▪ Loss of MMR</li> <li>▪ Treatment failure</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last molecular assessment (if no loss of MMR or treatment failure during follow-up)</li> <li>▪ Death</li> </ul>	Subjects in ITT (all randomized subjects) population that achieve MMR on Study
Duration of CHR (ITT population)	First confirmed CHR on study	<ul style="list-style-type: none"> <li>▪ Confirmed loss of CHR</li> <li>▪ Treatment failure</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last hematologic assessment (if no loss of CHR or treatment failure during follow-up)</li> <li>▪ Death</li> </ul>	Subjects in ITT (all randomized subjects) population that achieve CHR on Study
Time to progression to AP/BP (ITT population)	Randomization	<ul style="list-style-type: none"> <li>▪ First confirmed progression to AP or BP</li> <li>▪ Treatment failure</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last hematologic assessment (if no progression or treatment failure during follow-up)</li> <li>▪ Death</li> </ul>	ITT (all randomized subjects)

<b>Time to Event Endpoint</b>	<b>Initiating Event</b>	<b>Terminating Event(s) (if multiple terminating events, take earliest)</b>	<b>Censoring Event(s) (if multiple censoring events, take earliest)</b>	<b>Population</b>
EFS (ITT population)	Randomization	<ul style="list-style-type: none"> <li>▪ First confirmed progression to AP or BP</li> <li>▪ Doubling of WBC without CHR</li> <li>▪ First confirmed loss of CHR</li> <li>▪ Loss of CCyR</li> <li>▪ Death</li> </ul>	<ul style="list-style-type: none"> <li>▪ Last hematologic or cytogenetic assessment (if no progression or death during follow-up)</li> </ul>	ITT (all randomized subjects)

**Discussion (10/16/07):**

**Please see table 7.1, rows 2-4. Please clarify whether patients who are in CCyR, complete MR, and CHR are eligible for enrolment in this trial.**

Wyeth Response (10/22/07)

Patients in CCyR or complete MR are not eligible to enroll in the study. The rule in rows 2 and 3 were written to clarify how analysis would be done in the event that a patient was enrolled in violation of the eligibility criteria.

A patient in CHR could be enrolled in the study since treatment with hydroxyurea and anagrelide may result in a CHR.

FDA Discussion 10/23/07: FDA Agrees.

The primary analyses for the primary endpoint and secondary endpoints for which efficacy claims will be sought, and the plan for testing these secondary endpoints is summarized in Table 7-2.

Wyeth proposes that the analysis of the primary endpoint, testing the difference in CCyR rate at 1 yr between the two treatment arms, serve as the gatekeeper for two families of secondary hypotheses: short-term and long-term. If the primary analysis is significant, (1) the short-term family is tested via the fixed-sequence method at the 1-sided 0.025 level at the time of the primary analysis, and (2) the long-term family is tested via the Holm stepwise test at the 1-sided 0.025 level at the completion of long-term follow-up. This approach will strongly control the family-wise error rate for each family at the 1-sided 0.025 level.

Table 7-2: Endpoints intended to serve as basis for claims, prespecification of primary analyses, and testing plan.			
Endpoint Family	Endpoint	Method of Primary Analysis	Testing Plan
Primary	CCyR rate at 1 yr (48 wks) based on ITT population	Rate difference, large sample method, unpooled variance estimate.	1-sided test at 0.025 level when approximately 370 subjects have been evaluated for 1-yr CCyR rate (i.e., time of primary analysis).
Short-term Secondary Family	MMR rate at 1 yr (48 wks) based on ITT population	Rate difference, large sample method, unpooled variance estimate.	If the primary analysis is significant, this family is tested at the 1-sided family-wise level of 0.025 using a fixed-sequence method at the time of primary analysis. Each hypothesis is tested at the 1-sided 0.025 level, only if all previously tested hypotheses have been rejected at the 1-sided 0.025 level. The a priori ordering is (1) MMR rate, (2) CCyR rate in high risk subjects, and (3) TOI Fact-Leu score.
	CCyR rate at 1 yr (48 wks) based on ITT population of subjects with high-risk Sokal score at baseline	Odds ratio measure of treatment effect (logistic regression model)	
	TOI FACT-Leu score based on evaluable population	Effect of treatment on change from baseline in TOI Fact-Leu adjusted for baseline score and other baseline covariates, compared across arms via ANCOVA.	
Long-term Secondary Family	Duration of CCyR based on ITT population.	Hazard ratio measure of treatment effect (stratified Cox model)	If the primary analysis is significant, this family is tested at the 1-sided family-wise level of 0.025 using the Holm stepwise test at the completion of long-term follow-up.
	Duration of MMR based on ITT population	Hazard ratio measure of treatment effect (stratified Cox model)	
	Time to progression to AP/BP based on ITT population	Hazard ratio measure of treatment effect (stratified Cox model)	
	EFS based on ITT population	Hazard ratio measure of treatment effect (stratified Cox model)	
	Duration of CHR based on ITT population	Hazard ratio measure of treatment effect (stratified Cox model)	

**Discussion (10/16/07):**

- 1. The censoring schemes for the time to event endpoints are acceptable.**
- 2. Please clarify that after the primary endpoint is significant at 1-sided 0.025, you are planning to test the short-term family of secondary hypotheses at 1-sided 0.025 level and test the long-term family of secondary hypotheses at 1-sided 0.025 level after each secondary endpoint in the short-term family is significant at 1-sided 0.025 level.**

Wyeth Response (10/22/07)

Wyeth plans to use the short-term family of secondary hypotheses as the gatekeeper for the long-term family of secondary hypotheses. Thus, the long-term family of secondary hypotheses will be tested at the 1-sided 0.025 level only if each secondary endpoint in the short-term family is significant at the 1-sided 0.025 level.

FDA Discussion 10/23/07: FDA Agrees.

- 3. Please clarify that duration of response will be recorded as zero days for non-responders in the ITT analysis.**

Wyeth Response (10/22/07)

Wyeth agrees to record the duration of response as zero days for non-responders in the ITT analysis. As an exploratory analysis, Wyeth plans to conduct a conditional analysis of duration of response based on patients who respond to treatment.

FDA Discussion 10/23/07: FDA Agrees.

4. **Since this is an open-label trial the TOI FACT-leu score analysis will be considered exploratory.**

Wyeth Response (10/22/07)

Wyeth agrees to make the TOI FACT-Leu score analysis an exploratory rather than a secondary endpoint. The TOI Fact-Leu score will be deleted from the short-term family of secondary endpoints.

FDA Discussion 10/23/07: FDA Agrees.

The meeting was adjourned at 11:55 AM

Submitted by:

\_\_\_\_\_  
Carl Huntley, R.Ph., MBA  
Regulatory Project Manager

Concurrence:

\_\_\_\_\_  
John Johnson, M.D.  
Medical Team Leader

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John Johnson  
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<b>Sponsor Name:</b>	Wyeth Pharmaceuticals
<b>Application Number:</b>	IND 68268
<b>Product Name:</b>	Bosutinib (SKI-606)
<b>Meeting Type:</b>	Type B
<b>Meeting Category:</b>	Chemistry, Manufacturing and Controls, EOPII
<b>Meeting Date and Time:</b>	Thursday, 10 July, 2008 , 14:00- 15:00 ET
<b>Meeting Location:</b>	Food and Drug Administration, White Oak Campus, Silver Spring, MD
<b>Received Briefing Package</b>	20 June, 2008

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a **FACE- TO- FACE MEETING** on **Thursday, 10 July, 2008**, between **14:00** and **15:00 ET** between **Wyeth Pharmaceuticals**. and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Deborah Mesmer, Regulatory Health Project Manager for Quality, (301) 796-4023). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

## 1.0 BACKGROUND

Bosutinib (SKI-606) is a substituted 4-anilinoquinoline-3-carbonitrile inhibitor of Src and Abl kinases being developed by Wyeth for the treatment of (b) (4) previously treated (2<sup>nd</sup> line) Philadelphia Chromosome positive (Ph+) chronic myeloid leukemia (CML). The IND (68,268) for bosutinib was received on April 19, 2004. SKI-606 has been transitioned from the capsule formulation in the original IND to a tablet formulation prior to Phase III trials. A Type B, CMC EOPII meeting request to reach consensus on Wyeth's CMC plans for the development of a New Drug Application for SKI-606 was submitted and received on 23 April, 2008. The meeting was granted on 14 June, 2008, for a face-to-face meeting to be held on 10 July, 2008. The meeting briefing package was received on 20 June, 2008. The purpose of this document is to provide preliminary responses to the questions contained in the meeting briefing package. These responses are being archived and shared with Wyeth Pharmaceuticals to promote an efficient discussion at the meeting scheduled for 10 July, 2008.

## 2.0 SPONSOR QUESTIONS AND FDA PRELIMINARY RESPONSES

**Question 1: Does the Agency concur with Wyeth's identification of (b) (4) as the starting materials for the drug substance manufacturing process?**

**FDA Response to Question 1:** Insufficient information is provided to make a definitive assessment. The indicated compounds might be acceptable as regulatory starting materials, provided:

- (b) (4) is included as a starting material and adequate controls for its acceptance are provided
- In each starting material, the impurities are appropriately controlled or data are provided concerning why there is no need to control impurities in the raw material.
- For each starting material, the level of each impurity should be justified based on spiking and purging studies. In general, a genotoxic impurity should be controlled so that its level in the drug substance will be no more than the TTC level. Other impurities should be controlled at a level so that a non-genotoxic impurity present in a starting material should be sufficiently purged so that it (or its transformed secondary impurity) is at less than 0.1% level in the drug substance. If a genotoxic impurity is present (or produced during the drug substance synthesis), it should be reduced to below the TTC levels in the drug substance.
- Analytical methods for the starting materials should be shown to have sufficient resolution capability to detect and quantify all impurities. If need be, additional orthogonal methods may be employed to confirm the validity of a chosen analytical method. Similarly, the drug substance analytical method(s) should have adequate resolution capacity to detect and quantify process-related impurities as well as residual starting materials and the impurities in the starting materials.

**Additional Comment:**

- Some of the intermediates and raw materials, based on their structure, appear to be potentially genotoxic. Appropriate spiking and purging experiments and impurity fate analysis should be performed to assure the process is capable of purging the genotoxic impurities (as determined by DEREK analysis and / or Ames test) to below the TTC levels in the drug substance.

**Question 2: Does the Agency concur that the bridging strategy proposed to demonstrate the equivalence of the Wyeth (clinical) and (b) (4) (clinical/commercial) drug substance is adequate for NDA approval?**

**FDA Response to Question 2:** The approach appears to be acceptable.

- The impurity profiles of the batches used in clinical trials should be similar or better than the batches used in animal toxicology studies, and drug substance batches that are different, qualitatively or quantitatively, in impurity profiles should be adequately qualified in animal toxicology studies prior to their use in clinical studies. Summary data for such batches and studies should be submitted to the IND file.
- In addition to the comparison of the (b) (4) forms from the (b) (4) processes, justification for the presence of single desired (targeted) polymorph should also be provided based on (b) (4) considerations and stability. Whether there is a need to control the polymorphic content by a specification in the drug substance should be assessed based on ICH Q6A Decision tree # 4.

**Question 3: Does the Agency concur with Wyeth's proposal for assessing changes in the tablet formulation or manufacturing process made by (b) (4)**

**FDA Response to Question 3:** While the approach appears to be feasible, insufficient information is provided to make a definitive assessment.

- Provide the details of the single dose comparative bioavailability study performed to assess the two SKI-606 formulations, and the IVIVC study. Details should also provide information on whether or not the bioequivalence criteria were met and information regarding the power of the study.
- Provide details of the dissolution method and data to support that the dissolution method has adequate discrimination capability. Further, additional time points for dissolution data collection should be introduced between 0-30 minutes, to provide a better dissolution rate profile.
- In the IVIVC study, data and analysis should be provided to support a level C correlation between in-vitro and in-vivo parameters.

**Question 4: Does the Agency concur with the bridging strategy proposed to demonstrate the equivalence of the Wyeth (clinical) and (b) (4) (clinical/commercial) drug product is adequate for NDA approval?**

**FDA Response to Question 4:** The approach appears to be acceptable.

### 3.0 ISSUES REQUIRING FURTHER DISCUSSION

Additionally, we have the following comments:

- Clarify if the manufacturing process and equipment for various unit operations is similar at the Wyeth and (b) (4) drug product manufacturing sites.
- What are the shapes of the commercial tablets?
- Include specifications for content uniformity in the drug product.
- Clarify the type of (b) (4) operation employed for drug substance (b) (4). Also, clarification and appropriate justification should be provided whether the drug substance release testing is performed prior to or subsequent to the (b) (4) operation.
- Information / data concerning the (b) (4) should be provided. A (b) (4) should be included as release specification for the (b) (4).
- A thorough understanding of the relationships between material attributes, process parameters and CQA should be developed and documented in the NDA. Appropriate controls at the input stage and during the process should be in place to assure that product of purported quality attributes is manufactured with a high level of confidence at the commercial scale on a routine basis.
- You are encouraged to request a CMC-specific meeting pertaining to your QbD approach in the future.

### 4.0 CONCURRENCE:

*{See appended electronic signature page}*

Deborah Mesmer  
Regulatory Health Project Manager for Quality  
Division of Pre-Marketing Assessment III and Manufacturing Science  
Office of New Drug Quality Assessment  
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Ravi Harapanhalli, Ph.D.  
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Linked Applications

Sponsor Name

Drug Name

IND 68268

WYETH  
PHARMACEUTICALS  
INC

SKI-606

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/s/

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DEBORAH M MESMER

07/07/2008

RAVI S HARAPANHALLI

07/07/2008