

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206192Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206192

SUPPL # N/A

HFD # 107

Trade Name Cotellic

Generic Name cobimetinib

Applicant Name Genentech, Inc.

Approval Date, If Known November 10, 2015

### 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)

b) 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.

N/A

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:

N/A

c) Did the applicant request exclusivity?

YES  NO

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

Applicant included a statement claiming exclusivity under 21 C.F.R. §314.108(b)(2). Under information and belief, and further to a search of FDA records conducted on

20 November 2014, no drug product containing any active moiety including cobimetinib has previously been approved for commercial marketing under 505(b) of the FD&C Act. No years were specified in their statement.

d) 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?

N/A

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:



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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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MONICA L HUGHES  
11/10/2015

PATRICIA KEEGAN  
11/10/2015

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

NDA/BLA#: NDA 206192 Supplement Number: 0 NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DOP2 PDUFA Goal Date: Stamp Date: 12/11/2014  
12/11/2014

Proprietary Name: COTELLIC

Established/Generic Name: cobimetinib

Dosage Form: Tablets

Applicant/Sponsor: Genentech, Inc.

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

- (1) \_\_\_\_\_  
(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:** patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation, in combination with vemurafenib

**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:</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 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*

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@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 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 †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<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*

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

*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 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.)

**Section A: Fully Waived Studies (for all pediatric age groups)**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*

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

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) 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 †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<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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**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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MEREDITH LIBEG  
11/10/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206192 BLA #	NDA Supplement # N/A BLA Supplement #	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Cotellic Established/Proper Name: Cobimetinib Dosage Form: Tablet for oral use		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Meredith Libeg		Division: DOP2
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>November 11, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Kinase Inhibitor  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Fast Track            | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review        | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#) )**

- |   |  |
|---|--|
| NDAs: Subpart H   | BLAs: Subpart E  |
| <input type="checkbox"/> Accelerated approval (21 CFR 314.510)                | <input type="checkbox"/> Accelerated approval (21 CFR 601.41)    |
| <input type="checkbox"/> Restricted distribution (21 CFR 314.520)             | <input type="checkbox"/> Restricted distribution (21 CFR 601.42) |
| Subpart I   | Subpart H  |
| <input type="checkbox"/> Approval based on animal studies                     | <input type="checkbox"/> Approval based on animal studies        |
| <input type="checkbox"/> Submitted in response to a PMR                       | REMS: <input type="checkbox"/> MedGuide                          |
| <input type="checkbox"/> Submitted in response to a PMC                       | <input type="checkbox"/> Communication Plan                      |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU                                   |
|   | <input type="checkbox"/> MedGuide w/o REMS                       |
|   | <input type="checkbox"/> REMS not required                       |

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

### Action Letters

	Action(s) and date(s)
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	11/10/15 (corrected letter) 11/10/15 (original letter)

### Labeling

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Genentech</li> </ul>	<input type="checkbox"/> Included Genentech Proposed: 4/6/15 Original Genentech Proposed: 12/11/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included (Attached to Package Insert)
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included (Attached to Package Insert)
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Letter: 2/13/15 Final Review: 2/5/15
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None DMEPA: <input type="checkbox"/> None <ul style="list-style-type: none"> <li>11 2/15 (revised)</li> <li>5 20/15 (original)</li> </ul> DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> None SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None <ul style="list-style-type: none"> <li>Maternal Health: 7/9/15</li> </ul>

Administrative / Regulatory Documents	
<ul style="list-style-type: none"> <li>❖ RPM Filing Review<sup>4</sup>/Memo of Filing Meeting (<i>indicate date of each review</i>)</li> <li>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</li> </ul>	2/3/15 (Uploaded 12/2/15)  <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____                If PeRC review not necessary, explain: <b><u>Orphan designation granted</u></b></li> </ul> </li> </ul>	<b><u>Orphan designation granted</u></b>
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	N/A
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	Labeling: 11/9/15 (uploaded 11/10/15) Labeling T-con: 11/9/15 (uploaded 12/2/15) Labeling T-con: 11/6/15 (uploaded 12/2/15) PMR/PMC Doc: 11/5/15 Labeling T-con: 11/4/15 (uploaded 12/2/15) Labeling: 11/4/15 (uploaded 11/10/15) Labeling: 11/4/15 PMR/PMC Doc: 11/3/15 PMR/PMC Doc: 10/30/15 (uploaded 11/10/15) Labeling T-con: 10/30/15 Clinical IR: 10/30/15 Labeling T-con: 10/28/15 (uploaded 12/2/15) Labeling: 10/27/15 (uploaded 11/10/15)

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

	<p>Labeling: 10/20/15 (uploaded 11/10/15)  Labeling T-con: 10/8/15  <b>Major Amend Letter: 6/25/15</b>  Labeling/Clinical IR: 6/25/15  Clinical IR: 5/29/15  Labeling T-con: 5/28/15  <b>IR Letter: 5/20/15</b>  Clinical IR: 5/19/15  T-con: 5/15/15 (uploaded 12/2/15)  Clinical IR: 5/14/15  Clinical IR: 5/12/15  Clinical IR: 5/6/15  QT-IRT IR: 5/5/15  Clin Pharm IR: 4/3/15  NC IR: 4/2/15  QT-IRT IR: 3/25/15  Clin Pharm IR: 3/25/15  <b>Method Validation Letter: 3/24/15</b>  Clinical IR: 3/17/15  CMC IR: 3/6/15  Stats IR: 3/6/15  Clinical IR: 2/27/15  <b>Filing Letter: 2/23/15</b>  Method Validation IR: 2/23/15  <b>Prior Designation Letter: 2/13/15</b>  Clinical IR: 2/13/15  OSI IR: 2/11/15  OSE IR: 2/4/15  Clin Pharm IR: 2/4/15  T-Con Memo: 2/4/15 (Uploaded on 12/2/15)  Stats IR: 1/29/15  T-Con Memo: 1/28/15 (Uploaded on 11/23/15)  Clinical IR: 1/28/15  <b>Ack Letter: 1/5/15</b>  <b>AOM Letter: 12/19/14</b>  <b>Pre-sub Ack Letter: 11/19/14/14</b></p>
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	<p>Clinical IR MTF: 3/18/15 (uploaded 11/23/15)  Clinical IR MTF: 1/29/15 (uploaded 11/23/15)</p>
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul> </li> </ul>	<p>Multidiscipline: 10/8/14 (uploaded 10/29/14)  CMC only: 3/5/14 (Upload 3/12/14)</p>
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> No mtg

	CMC only: 11/27/12 (Upload 11/28/12)
	Multidiscipline: 6/27/12 (uploaded 7/26/12)
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A 3/23/15
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A 5/20/15
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	Type C WRO: 11/29/13 Type C WRO: 4/22/13
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Final Review: 11/9/15
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Final Review: 11/05/15 Designation MTF: 2/13/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Final review: 11/10/15
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None PMR (Clinical): 12/3/15 PMC (Clinical): 12/3/15 PMR (Clin Pharm): 11/13/15
<b>Clinical</b>	
❖ Clinical Reviews	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	Final review: Concurred on 11/1/15 - See clinical final review Filing Review: Concurred on 2/6/15 - See clinical filing review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	Final Review: 10/31/15 Filing Review: 2/4/15
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Final review: See Clinical Review: (Page 41 to 42)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Ophthalmology Final Review: 6/3/15 QT-IRT Final Review: 5/8/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> N/A Final review: 11/3/15
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> <li>•</li> </ul>	N/A N/A <input type="checkbox"/> None Final review: 5/26/15
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested OSI Letter (Liszkay): 11/5/15 OSI Letter (Ascierto): 10/6/15 OSI Letter (Maio): 10/6/15 OSI Letter (Ferraresi): 9/8/15 OSI Letter (Clark): 7/10/15 Final review: 5/27/15
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Final review addendum: Concurred on 11/2/15 - See Stats final review addendum Final review: Concurred on 5/11/15 - See Stats final review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Final review addendum: Concurred on 11/2/15 - See Stats final review addendum Final review: Concurred on 5/7/15 - See Stats final review

	Filing Review: Concurred on 1/26/15 - See Stats filing review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None  Final review addendum: 11/2/15  Final review: 5/6/15  Filing Review: 1/26/15
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review  Final review: see Integrated review <ul style="list-style-type: none"> <li>• Clin Pham: Concurred on 5/11/15</li> <li>• Pharmacometrics: Concurred on 5/11/15</li> </ul>
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review  Final review: see Integrated review <ul style="list-style-type: none"> <li>• Clin Pham: Concurred on 5/11/15</li> <li>• Pharmacometrics: Concurred on 5/11/15</li> </ul> Filing Review: Concurred on 2/10/15 - See Clin Pharm filing review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None  Final review: Integrated review <ul style="list-style-type: none"> <li>• Clin Pham: 5/10/15</li> <li>• Pharmacometrics: 5/11/15</li> </ul> Filing Review: 2/10/15
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> <li>• ADP/T Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review  Final review: 10/28/15
<ul style="list-style-type: none"> <li>• Supervisory Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review  Final review: Concurred on 5/29/15 - See NC Final review and Supervisory Memorandum of 5/29/15  Filing Review: Concurred on 2/3/15 - See NC filing review
<ul style="list-style-type: none"> <li>• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None  Final review: 5/29/15

	Filing Review: 2/2/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Final Review: Concurred on 5/11/15 - See Integrated Quality Assessment review
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Final review: All reviewers signatures dated 5/11/15 <ul style="list-style-type: none"> <li>• Drug substance</li> <li>• Drug Product</li> <li>• Process/Microbiology</li> <li>• Facilities:</li> <li>• Biopharmaceutics</li> <li>• Business Process Manager</li> <li>• ORA Lead</li> <li>• Environment Assessment:</li> </ul> Filing Review: 3/5/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Method Validation: 5/21/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See page 84 of the Integrated Quality Assessment review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable: (See pages 53 to 59 of the Integrated Quality Assessment review) Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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MEREDITH LIBEG  
12/03/2015



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

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Memorandum

**Date:** February 4, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Sponsor Teleconference – Clinical and Statistical Dataset Meeting*

---

Date and Time of Teleconference: February 4, 2015, approximately 3:30 p.m. to 4:00 p.m.

**FDA Participants:**

Ruthann Giusti, M.D.	Clinical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

**Sponsor Participants:**

Cynthia Nguyen, Pharm.D.	Regulatory Affairs, Program Manager
Ilsung Chang, Ph.D.	Biostatistics, Lead
Jessie Hsu, Ph.D.	Biostatistics
Nilesh Narayan	Regulatory Operations
Nalin Tikoo, M.S.	Biometrics, Lead
Nageshwar Budha, Ph.D.	Clinical Pharmacology
Sarah Wayson, Ph.D.	U.S. Regulatory Lead

---

This was an FDA-initiated teleconference to discuss the clinical and statistical aspects of the datasets submitted on December 11, 2014, in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.

**Summary of the TCON:**

FDA and Genentech discussed the clinical and statistical aspects of the datasets submitted on December 11, 2014, specifically where to locate specific information contained in the NDA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification.

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12/02/2015



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Memorandum

**Date:** October 28, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Sponsor Teleconference – Labeling*

---

Date and Time of Teleconference: October 28, 2015, approximately 11:00 a.m. to 12:00 p.m.

**FDA Participants:**

Patricia Keegan, M.D.	Division Director
Marc Theoret, M.D.	Clinical Team Leader
Ruthann Giusti, M.D.	Clinical Reviewer
Kun He, Ph.D.	Statistical Team Leader
Xiaoping (Janet) Jiang, Ph.D.	Statistical Reviewer
Hong Zhao, Ph.D.	Clinical Pharmacology Team leader
Ruby Leong, Ph.D.	Clinical Pharmacology Reviewer
Olen Stephens, Ph.D.	CMC Team Leader
Whitney Helms, Ph.D.	Nonclinical Team Leader
Shawna Weis, Ph.D.	Nonclinical Reviewer
Monica Hughes, M.S.	Chief Project Management Staff
Meredith Libeg	Senior Regulatory Project Manager

**Sponsor Participants:**

Sarah Wayson, Ph.D.	U.S. Regulatory Lead
Dora Lambros, M.S.	U.S. Regulatory Program Manager
Brisdell Hunte	Global Development Team Lead
Josina Reddy, M.D., Ph.D.	Clinical Science, Senior Director
Nicholas Choong, M.D.	Lead Clinician for cobimetinib
Jason Erlich, M.D.	Clinical Science (ophthalmology), Director
Steve Slater, Ph.D.	Regulatory Affairs, Senior Director
Seema Shah	Global Regulatory Lead
Jenny Huang, Ph.D.	Biostatistical Senior Director
Ilsung Chang, Ph.D.	Biostatistical Lead
Susan Eng, Pharm.D.	Safety Science Lead
Luna Musib, Ph.D.	Clinical Pharmacology Lead
Edna Choo, Ph.D.	Metabolism and Pharmacokinetics, Lead
Eric Harstad, Ph.D.	Toxicology Lead
Mark Merchant, Ph.D.	Research Lead

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NDA 206192  
Teleconference 10/28/15

This was an FDA-initiated teleconference (TCON) to discuss the proposed package insert in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation submitted on December 11, 2014. In advance of this meeting, Genentech provided their counter-proposed labeling for discussion during the meeting.

Summary of the TCON:

FDA thanked Genentech for agreeing to the meeting and noted that the goal of the meeting was to discuss the proposed labeling. FDA and Genentech both provided detailed explanations for their proposals to the revised sections; and FDA noted what would and would not be acceptable for inclusion in the package insert.

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12/02/2015



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Memorandum

**Date:** November 9, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** **NDA 206192 – Genentech, Inc. (Genentech)**  
***Sponsor Teleconference – Labeling***

---

Date and Time of Teleconference: November 9, 2015, approximately 2:30 p.m. to 3:00 p.m.

**FDA Participants:**

Patricia Keegan, M.D.	Division Director
Marc Theoret, M.D.	Clinical Team Leader
Ruthann Giusti, M.D.	Clinical Reviewer
Meredith Libeg	Senior Regulatory Project Manager

**Sponsor Participants:**

Sarah Wayson, Ph.D.	U.S. Regulatory Lead
Dora Lambros, M.S.	U.S. Regulatory Program Manager
Brisdell Hunte	Global Development Team Lead
Josina Reddy, M.D., Ph.D	Clinical Science, Senior Director
Nicholas Choong, M.D.	Lead Clinician for cobimetinib
Steve Slater, Ph.D.	Regulatory Affairs, Senior Director
Seema Shah	Global Regulatory Lead
Ilsung Chang, Ph.D.	Biostatistical Lead
Susan Eng, Pharm.D	Safety Science Lead
Luna Musib, Ph.D.	Clinical Pharmacology Lead
Cynthia Nguyen, Pharm.D.	Regulatory US Regulatory
Nataliya Chernyukhin, M.D.	Safety Group Director

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This was an FDA-initiated teleconference (TCON) to discuss the proposed package insert in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation submitted on December 11, 2014.

**Summary of the TCON:**

FDA thanked Genentech for agreeing to the meeting and noted that the goal of the meeting was to discuss the proposed labeling and reach potential agreement on the proposed labeling. FDA and Genentech both provided detailed explanations for their proposals to the revised sections; and FDA noted what would and would not be acceptable for inclusion in the package insert.

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Memorandum

**Date:** November 6, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** **NDA 206192 – Genentech, Inc. (Genentech)**  
***Sponsor Teleconference – Labeling***

Date and Time of Teleconference: November 6, 2015, approximately 4:00 p.m. to 4:30 p.m.

**FDA Participants:**

Patricia Keegan, M.D.	Division Director
Marc Theoret, M.D.	Clinical Team Leader
Ruthann Giusti, M.D.	Clinical Reviewer
Meredith Libeg	Senior Regulatory Project Manager

**Sponsor Participants:**

Sarah Wayson, Ph.D.	U.S. Regulatory Lead
Dora Lambros, M.S.	U.S. Regulatory Program Manager
Brisdell Hunte	Global Development Team Lead
Josina Reddy, M.D., Ph.D.	Clinical Science, Senior Director
Nicholas Choong, M.D.	Lead Clinician for cobimetinib
Ilsung Chang, Ph.D.	Biostatistical Lead
Susan Eng, Pharm.D	Safety Science Lead
Luna Musib, Ph.D.	Clinical Pharmacology Lead
Nataliya Chernyukhin, M.D.	Safety Group Director
Jenny Huang, Ph.D.	Biostatistics Senior Director

This was an FDA-initiated teleconference (TCON) to discuss the proposed package insert in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation submitted on December 11, 2014. In advance of this meeting, FDA provided their counter-proposed labeling for discussion during the meeting.

**Summary of the TCON:**

FDA thanked Genentech for agreeing to the meeting and noted that the goal of the meeting was to discuss the proposed labeling. FDA and Genentech both provided detailed explanations for their proposals to the revised sections; and FDA noted what would and would not be acceptable for inclusion in the package insert.

**Attachments:**

- FDA proposed package insert of 11.6.15

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Memorandum

**Date:** November 4, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** **NDA 206192 – Genentech, Inc. (Genentech)**  
***Sponsor Teleconference – Labeling/PMR Discussion***

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Date and Time of Teleconference: November 4, 2015, approximately 2:30 p.m. to 4:00 p.m.

**FDA Participants:**

Marc Theoret, M.D.	Clinical Team Leader
Ruthann Giusti, M.D.	Clinical Reviewer
Wiley Chambers, M.D.	Deputy Director, DTOP
Jennie Chang, Pharm.D.	Labeling Reviewer
Olen Stephens, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Team Leader, OPQ
Whitney Helms, Ph.D.	Pharmacology/Toxicology Team Leader, DHOT
Kun He, Ph.D.	Biometrics Team Leader OBV
Xiaoping (Janet) Jiang, Ph.D.	Biometrics Reviewer, OBV
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCPV
Ruby Leong, Ph.D.	Clinical Pharmacology Reviewer, DCPV
Jeffery Summers, M.D.	Deputy Director for Safety, DOP2
Meredith Libeg	Senior Regulatory Project Manager

**Sponsor Participants:**

Sarah Wayson, Ph.D.	U.S. Regulatory Lead
Dora Lambros, M.S.	U.S. Regulatory Program Manager
Brisdell Hunte	Global Development Team Lead
Josina Reddy, M.D., Ph.D.	Clinical Science, Senior Director
Nicholas Choong, M.D.	Lead Clinician for cobimetinib
Ilsung Chang, Ph.D.	Biostatistical Lead
Susan Eng, Pharm.D.	Safety Science Lead
Luna Musib, Ph.D.	Clinical Pharmacology Lead
Jenny Huang, Ph.D.	Biostatistics Senior Director
Steve Slater Ph.D.	Regulatory Affairs, Senior Director
Seema Shah	Global Regulatory Lead
Edna Choo, Ph.D.	Metabolism and Pharmacokinetics, Lead
Eric Harstad, Ph.D.	Toxicology Lead
Jason Ehrlich M.D.	Clinical Science (Ophtho)
Cynthia Nguyen, Pharm.D.	Regulatory US Regulatory

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This was an FDA-initiated teleconference (TCON) to discuss the proposed package insert in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation submitted on December 11, 2014. In advance of this meeting, FDA provided their counter-proposed labeling for discussion during the meeting.

Summary of the TCON:

FDA thanked Genentech for agreeing to the meeting and noted that the goal of the meeting was to discuss the proposed labeling. FDA and Genentech both provided detailed explanations for their proposals to the revised sections; and FDA noted what would and would not be acceptable for inclusion in the package insert.

In addition to the discussion on labeling, FDA and Genentech further negotiated the proposed PMR for ocular toxicity. During the meeting, FDA explained the intent of the PMR (question the PMR was to address) and what would be required for this PMR. Genentech provided detailed explanations for their counterproposal provided via email communication on November 3, 2015 (to be followed with a formal submission to the NDA). After further discussion, FDA agreed to provide a counterproposal of the PMR language to Genentech for negotiations and potential agreement.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
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Memorandum

**Date:** May 15, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Sponsor Teleconference – Clinical and Statistical Dataset Meeting*

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Date and Time of Teleconference: May 15, 2015, approximately 2:00 p.m. to 2:30 p.m.

**FDA Participants:**

Marc Theoret, M.D.	Clinical Team Leader, DOP2
Ruthann Giusti, M.D.	Clinical Reviewer
Meredith Libeg	Regulatory Health Project Manager, DOP2

**Sponsor Participants:**

Cynthia Nguyen, Pharm.D.	Regulatory Affairs, Program Manager
Ilsung Chang, Ph.D.	Biostatistics, Lead
Nalin Tikoo, M.S.	Biometrics, Lead
Sarah Wayson, Ph.D.	U.S. Regulatory Lead
Brisdell Hunte (BH), M.S.	Global Regulatory Lead
Nicholas Choong (NC), M.D.	Lead Clinician for cobimetinib
Isabelle Rooney (IR), M.D.	Clinical Science
Susan Eng (SE) Pharm. D.	Safety Lead

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This was an FDA-initiated teleconference to discuss the clinical aspects of the datasets submitted on December 11, 2014, and the 90-day safety updated submitted on March 10, 2015, in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.

**Summary of the TCON:**

FDA and Genentech discussed the clinical aspects of the datasets submitted on December 11, 2014, and the 90-day safety updated submitted on March 10, 2015. Specifically, FDA sought clarification on discrepancies between the original safety submission and the updated safety submission, in which 8 patients from the GO28141 study were reassigned treatment arms. Genentech provided a detailed explanation noting the reassignment of treatment arms was because of data entry errors found during regulator monitoring visits at the sites. Genentech continued by stating that each study drug kit had a unique random identification number, which was recorded by the study coordinator in the eCRF after dispensing to the patient. During monitoring visitors, the clinical monitor for the study would review the unique identification code on the retained study drug kit and verified against the eCRF entry. It was during this process that the data entry errors were found and corrected. FDA acknowledged Genentech's explanation, but noted that further requests for information may be further coming, in a separate communication, in order to ensure that the data provided is accurate.

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Memorandum

**Date:** January 29, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Memorandum relating to Clinical Review Comments and Information  
Request dated January 28, 2015*

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**Background:**

On January 28, 2015, FDA initiated a request for information via email communication relating to clinical aspects contained in submission dated December 11, 2014, in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. Upon receipt of the of the clinical information request, Genentech requests clarification. This memorandum provides information on the request for clarification and the final result of that request.

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Upon receipt of the of the clinical information request dated January 28, 2015, Genentech sought clarification. This request for clarification was received on January 28, 2015, via email.

FDA comment of January 28, 2015: “Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? If so, where in the application can this information be found? Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? If so, where in the application can this information be found?”

Genentech request for clarification of January 28, 2015: Can FDA clarify foreign studies justification request.

Upon receipt of the request for clarification, FDA discussed internally and provided the following clarification to Genentech via email on January 29, 2015:

FDA clarification of January 29, 2015: Provide a subgroup analysis comparing US vs Non-US sites for investigator determined PFS.

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**Conclusion:**

Genentech concluded that the clarification was clear and agreed to address the request for information in the requested timeframe.

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11/23/2015



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Memorandum

**Date:** March 18, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Memorandum relating to NDA 206192 submission dated March 18, 2015*

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**Background:**

On March 12, 2015, Genentech initiated a request for clarification via email communication relating to clinical aspects in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation submitted on dated December 11, 2014. Genentech queried if the amended protocol and amended statistical analysis plan for Study GO28141 (coBRIM), the pivotal study supporting NDA 206192, should be submitted in duplicate to the NDA or only be submitted to the cross referenced IND. Upon receipt of the request for information, FDA discussed internally.

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**Conclusion:**

On March 13, 2015, FDA concluded that the amended protocol and amended statistical analysis plan for Study GO28141 (coBRIM) should be submitted to both the NDA and the cross referenced IND.

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Memorandum

**Date:** January 28, 2015  
**From:** Meredith Libeg, Regulatory Health Project Manager-CDER/OHOP/DOP2  
**Subject:** **NDA 206192 – Genentech, Inc. (Genentech)**  
***Sponsor Face-To-Face/Teleconference – Clinical and Statistical Dataset Meeting***

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Date and Time of Face-To-Face/Teleconference: January 28, 2015, 12:00 p.m. to 1:00 p.m.

**FDA Participants:**

Marc Theoret, M.D. Clinical Team Leader  
Ruthann Giusti, M.D. Clinical Reviewer  
Xiaoping (Janet) Jiang, Ph.D. Statistical Reviewer  
Meredith Libeg Regulatory Health Project Manager, DOP2

**Sponsor Participants (Present in Person):**

Cynthia Nguyen, Pharm.D. Regulatory Affairs, Program Manager  
Ilsung Chang, Ph.D. Biostatistics, Lead  
Jessie Hsu, Ph.D. Biostatistics  
Nilesh Narayan Regulatory Operations  
Nalin Tikoo, M.S. Biometrics, Lead

**Sponsor Participants (Present via Teleconference):**

Stephen Hack, M.D., Ph.D. Clinical Lead  
Nageshwar Budha, Ph.D. Clinical Pharmacology  
Doris Karkazis Regulatory Manager  
Sarah Wayson, Ph.D. U.S. Regulatory Lead

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This was an FDA-initiated Face-to-Face to discuss the clinical and statistical aspects of the datasets submitted on December 11, 2014, in support of the pending NDA 206192 for Cotellic (proposed proprietary name) (cobimetinib) for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. Due to the timing of the meeting, several Genentech participants joined via teleconference.

**Summary of the TCON:**

FDA and Genentech discussed the clinical and statistical aspects of the datasets submitted on December 11, 2014, specifically where to locate specific information contained in the NDA, how variables within the datasets are defined, and verbal response to FDA questions and requests for clarification. Information that required Genentech's follow-up internally in order to address the question/inquiry, are captured below and responses will be provided via email communication to FDA; and followed by Genentech's formal submission to the NDA.

Items Requiring Genentech's Follow-up:

1. Please clarify the difference of 252 adverse events (AEs) from the 6980 AEs in the SDTM AE dataset and 6728 AEs in the ADAE dataset for Study GO28141.
2. Please provide clarification on reconciliation of death events in GO28141 as 97 patients had death tags and values calculated. 2 events of death were not reflected in the DM dataset.
3. Please provide the source datasets for the generation of Table 8 in CSR GO28141.
4. Please clarify the DSDTC variable and date of progression from Studies GO28141 and NO25395.

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/s/  
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MEREDITH LIBEG  
11/23/2015

## Libeg, Meredith

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**From:** Libeg, Meredith  
**Sent:** Friday, October 30, 2015 7:53 PM  
**To:** 'Sarah Wayson'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA Proposed PMR/PMCs  
**Attachments:** NDA 206192 Proposed PMC-PMR Language\_October 30, 2015.pdf

**Importance:** High

Hi Sarah,

Please find attached a memorandum containing FDA's proposed post-marketing requirements and post-marketing commitments relating to your NDA application (NDA 206192) submitted on December 11, 2014. We are requesting a response to our proposals by noon on Tuesday, November 3<sup>rd</sup>, or sooner if possible.

While reviewing, please note that we have not included the PMC relating to the device as discussed at today's meeting. Additionally, we are still discussing whether a PMR/PMC will be required by the Controlled Substance Staff as mentioned during the late cycle meeting. Relating to both these items, we will be in touch early next week.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721



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

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Memorandum

**Date:** October 30, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc. (Genentech)  
*Proposed PMC/PMR Language*

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

Please see FDA’s post-marketing requirements and post-marking commitments proposal. Please provide your responses via email communication by noon on Tuesday, November 3, 2015, or sooner if possible.

**Post Marketing Requirements (PMRs) Under 505(o)**

**CLINICAL PHARMACOLOGY**

**Hepatic Impairment Pharmacokinetic Study:**

1. Complete a pharmacokinetic study to determine the appropriate dose of cobimetinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

**Final Protocol Submission:**

**Trial Completion Date:**

**Final Report Submission:**

## **CLINICAL**

### **Ocular Toxicity:**

2. Provide an integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using cobimetinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED) and subsequent sequelae, including the frequency, time course and if needed, dose alternation required to minimize the impact of retinal pigmented epithelial detachments including safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

**Final Protocol Submission:**

**Trial Completion Date:**

**Final Report Submission:**

## **POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

## **CLINICAL**

### **Clinical Trial To Further Define the Efficacy of Cobimetinib:**

3. Submit the clinical study report at the time of the final analysis of Trial GO28141, A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus Cobimetinib (GDC-0973) in Previously Untreated BRAFV600-Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma (coBRIM) to inform the label with mature overall survival data.

**Final Report Submission:**

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, Structure and Content of Clinical Reports  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>.
- Guidance for Industry, entitled, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>.

- Guidance for Industry, entitled, Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
- Guidance for Industry, entitled, Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
11/10/2015

## Libeg, Meredith

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**From:** Libeg, Meredith  
**Sent:** Tuesday, October 20, 2015 6:40 PM  
**To:** 'Sarah Wayson'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA Proposed Labeling Edits (10.20.15)  
**Attachments:** FDA Proposed labeling for Cobimetinib 10.20.15.docx

**Importance:** High

Hi Sarah

Please find attached FDA's first round of proposed edits to the Cobimetinib PI relating to your NDA 206192 submitted on December 11, 2014.

Please note that everything FDA has agreed with to your proposed modifications, we have accepted your edits to the document. Please review our edits and comments and determine if you are in agreement with the proposed edits. If you have edits to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. When making edits to the label, please update formatting as necessary.

Please submit the updated labeling via email by COB on Tuesday, October 27, 2015, or sooner if possible; and follow with a formal submission to the NDA. As previously mentioned, we are hoping to schedule a meeting to discuss the labeling next week.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MEREDITH LIBEG  
11/10/2015

## Libeg, Meredith

---

**From:** Libeg, Meredith  
**Sent:** Wednesday, November 04, 2015 1:30 AM  
**To:** Sarah Wayson; 'Cynthia Nguyen'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA Proposed Labeling Edits (11.4.15)  
**Attachments:** FDA Proposed labeling for Cobimetinib\_GENENTECH-RESPONSE-11.4.15.docx

**Importance:** High

Hi Sarah and Cynthia,

Please find attached FDA's next round of proposed edits to the Cobimetinib PI relating to your NDA 206192 submitted on December 11, 2014 in preparation for the teleconference scheduled for November 4, 2015 from 2:30 PM ET.

Please note that everything FDA has agreed with to your proposed modifications, we have accepted your edits to the document. Please review our edits and comments and determine if you are in agreement with the proposed edits. If you have edits to propose, please accept all edits that you are in agreement with. Any additional edits/modifications to the document you wish to make should be displayed using track-changes within this version of the document. Additionally, please provide a comment with the justification of the proposed change. When making edits to the label, please update formatting as necessary.

Following the call, we will discuss next steps.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721

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/s/  
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MEREDITH LIBEG  
11/10/2015

## Libeg, Meredith

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**From:** Libeg, Meredith  
**Sent:** Monday, November 09, 2015 1:58 PM  
**To:** 'Sarah Wayson'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA proposed Labeling Edits (11.9.15)  
**Attachments:** FDAProposedEdits\_COTELLIC-GENENTECH-20151109\_REDLINED.docx

**Importance:** High

Hi Sarah,

In preparation for today's teleconference at 2:30 PM ET, please find attached FDA's proposed labeling for NDA 206192 for discussion. We are hoping to come to final agreement during the call. When you send back the labeling following the meeting, please place in the November 2015 at in the PPI and in the Highlights.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MEREDITH LIBEG  
11/10/2015

## Libeg, Meredith

---

**From:** Libeg, Meredith  
**Sent:** Tuesday, October 27, 2015 12:04 AM  
**To:** 'Sarah Wayson'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA Proposed Carton and Container Edits (10.27.15)  
**Attachments:** Draft Carton and Container Labels FDA version 10.27.15.pdf  
**Importance:** High

Hi Sarah

Please find attached FDA's proposed edits to the Cobimetinib carton and container relating to your NDA 206192 submitted on December 11, 2014.

Please submit your response via email by COB on Friday, October 30, 2015, or sooner if possible; and follow with a formal submission to the NDA.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721

1.14.1.1 Draft Carton and Container Labels

DRAFT TEXT  
COBIMETINIB 20 MG BOTTLE LABEL (10158595)  
Label Dimensions = 95 mm x 35 mm

1. FRONT PANEL  
NDC 50242-717-01

**Tradename™**  
(cobimetinib) tablets

**20 mg**

Rx only

63 tablets

[Genentech (b) (4)]

2. LEFT SIDE PANEL

Each film-coated tablet contains 20 mg cobimetinib (22 mg as cobimetinib (b) (4) fumarate salt).

**Usual dosage:** (b) (4)

**Store at** (b) (4) **below 30°C (86°F).**

(b) (4)

**EXP**  
**Lot**

3. RIGHT SIDE PANEL

Made in Switzerland

Distributed by:  
**Genentech USA, Inc.**  
A Member of the Roche Group  
South San Francisco, CA 94080-4990

[Bar code and human readable “N3 50242-717-01 4” will be printed on label]

(b) (4)



**DRAFT LABEL TEXT**  
**COBIMETINIB 20 MG CARTON (10158589)**

Carton Dimensions = 70 mm x 50 mm x 90 mm (L×W×H)

**1. TOP PANEL**

**Tradename™**  
(cobimetinib) tablets

**20 mg**

[ (b) (4) ] 63 tablets

[Genentech (b) (4)]

**2. FRONT PANEL**

NDC 50242-717-01

**Tradename™**  
(cobimetinib)  
tablets

**20 mg**

Rx only

63 tablets

[ (b) (4) ]

[Genentech (b) (4)]

[ (b) (4) ]

[ (b) (4) ]

**3. LEFT SIDE PANEL**

Each film-coated tablet contains 20 mg cobimetinib (22 mg as cobimetinib (b) (4) fumarate salt).

**Usual dosage:** (b) (4)

**Store at** (b) (4) **below 30°C (86°F).**

[Roche Griffin logo]

Made in Switzerland

Distributed by:

**Genentech USA, Inc.**

A Member of the Roche Group

South San Francisco, CA

94080-4990

**4. LEFT SIDE PANEL – TUCK FLAP**

(b) (4)

**5. RIGHT SIDE PANEL**

**Tradename™**

(cobimetinib)

tablets

**20 mg**

63 tablets

(b) (4)

[Genentech (b) (4)]

**6. BACK PANEL**

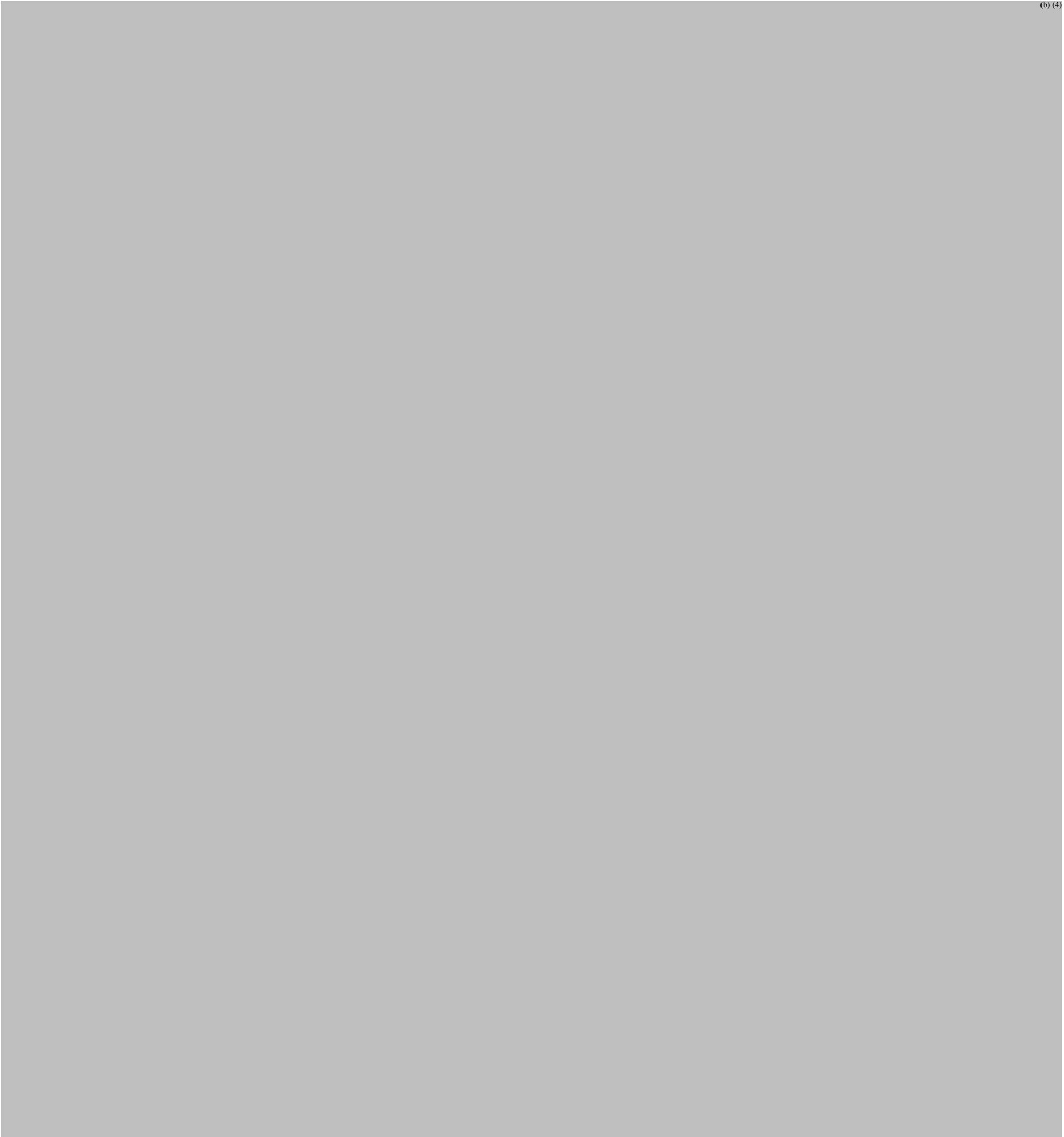
[UPC bar code and human readable “N3 50242-717-01 4” will be printed on this panel]

**7. BOTTOM PANEL**

EXP

Lot

(b) (4)



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/s/  
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MEREDITH LIBEG  
11/10/2015



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

---

Memorandum

**Date:** October 30, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Proposed PMC/PMR Language*

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

Please see FDA’s post-marketing requirements and post-marking commitments proposal. Please provide your responses via email communication by noon on Tuesday, November 3, 2015, or sooner if possible.

**Post Marketing Requirements (PMRs) Under 505(o)**

**CLINICAL PHARMACOLOGY**

**Hepatic Impairment Pharmacokinetic Study:**

1. Complete a pharmacokinetic study to determine the appropriate dose of cobimetinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

**Final Protocol Submission:**  
**Trial Completion Date:**  
**Final Report Submission:**

## **CLINICAL**

### **Ocular Toxicity:**

2. Provide an integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using cobimetinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED) and subsequent sequelae, including the frequency, time course and if needed, dose alternation required to minimize the impact of retinal pigmented epithelial detachments including safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

**Final Protocol Submission:**

**Trial Completion Date:**

**Final Report Submission:**

## **POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

### **CLINICAL**

#### **Clinical Trial To Further Define the Efficacy of Cobimetinib:**

3. Submit the clinical study report at the time of the final analysis of Trial GO28141, A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus Cobimetinib (GDC-0973) in Previously Untreated BRAFV600-Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma (coBRIM) to inform the label with mature overall survival data.

**Final Report Submission:**

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, Structure and Content of Clinical Reports  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>.
- Guidance for Industry, entitled, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>.

- Guidance for Industry, entitled, Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

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If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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*/s/*

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MEREDITH LIBEG  
11/10/2015

## Libeg, Meredith

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**From:** Libeg, Meredith  
**Sent:** Thursday, November 05, 2015 1:38 PM  
**To:** Sarah Wayson; 'Cynthia Nguyen'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA Proposed PMR/PMCs  
**Attachments:** NDA 206192 Proposed PMC-PMR Language\_November 5, 2015.pdf

**Importance:** High

Hi Sarah and Cynthia,

As discussed at yesterday's meeting, please find attached a memorandum containing FDA's revised proposed post-marketing requirement for ocular toxicity relating to your NDA application (NDA 206192) submitted on December 11, 2014. We are requesting a response to our proposal by noon on Friday, November 6th, or sooner if possible.

In order to assist in the milestone scheduling for this PMR, we would recommend including appropriate buffer time for contingencies and to include due diligence in determining milestones. We would also encourage you to have the actual group that will be responsible for doing the trials and studies are involved in providing input into the milestone schedule when proposing the milestones schedule.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721



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

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Memorandum

**Date:** November 5, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc. (Genentech)  
**Proposed PMR Language**

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

Please see FDA’s counterproposal for post-marketing requirements as discussed at the November 4, 2015, meeting. Please provide your response via email communication by noon on Friday, November 6, 2015, or sooner if possible.

**Post Marketing Requirement (PMR) Under 505(o)**

**CLINICAL**

**Ocular Toxicity:**

1. Provide an integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using cobimetinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED) and subsequent sequelae, including the frequency, time course and if needed, dose alteration required to minimize the impact of retinal pigmented epithelial detachments. This will include safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

**Final Protocol Submission:**  
**Trial Completion Date:**  
**Submission Timeline:**

To assist you in organizing the submission of final study reports, we refer you to the following resources:

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>.
- Guidance for Industry, entitled, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>.
- Guidance for Industry, entitled, Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
- Guidance for Industry, entitled, Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act  
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Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

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/s/  
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MEREDITH LIBEG  
11/05/2015



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

---

Memorandum

**Date:** November 5, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Proposed PMR Language*

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

Please see FDA’s counterproposal for post-marketing requirements as discussed at the November 4, 2015, meeting. Please provide your response via email communication by noon on Friday, November 6, 2015, or sooner if possible.

**Post Marketing Requirement (PMR) Under 505(o)**

**CLINICAL**

**Ocular Toxicity:**

1. Provide an integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using cobimetinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED) and subsequent sequelae, including the frequency, time course and if needed, dose alteration required to minimize the impact of retinal pigmented epithelial detachments. This will include safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

**Final Protocol Submission:**  
**Trial Completion Date:**  
**Submission Timeline:**

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, Structure and Content of Clinical Reports  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>.
- Guidance for Industry, entitled, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>.
- Guidance for Industry, entitled, Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
- Guidance for Industry, entitled, Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
11/05/2015



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

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Memorandum

**Date:** November 4, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
*Carton and Container Labeling Comments and Information Request*

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

Our Reviewers have the following request for information relating to the carton and container labeling. Please provide your response to me via email as soon as possible, and follow that with a formal submission to the NDA.

**Comments:**

1. FDA proposes to revise the following statement from “Usual dosage: [REDACTED] (b) (4) [REDACTED]” to “Usual Dosage: See prescribing information.”

This dosage regimen may be unique to the Genentech product line, but is not unique to health care professionals who provide services to oncology patients; therefore, FDA recommends the more general statement noted above which requires less space on the side panel of the container label.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
11/04/2015

## Libeg, Meredith

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**From:** Libeg, Meredith  
**Sent:** Tuesday, November 03, 2015 8:32 PM  
**To:** 'Sarah Wayson'  
**Cc:** 'Cynthia Nguyen'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA Proposed PMR/PMCs  
**Attachments:** NDA 206192 Proposed PMC-PMR Language\_November 3, 2015.pdf

Hi Sarah and Cynthia,

Please find attached a memorandum containing FDA's additional proposed post-marketing commitment relating to your NDA application (NDA 206192) submitted on December 11, 2014. We are requesting a response to our proposal by noon on Thursday, November 5<sup>th</sup>, or sooner if possible.

While reviewing, please note that a controlled substance PMR/PMC is not proposed at this time. After discussions internally with the controlled substance staff (CSS), it has been determined that neither a PMR nor a PMC will be required at this time relating to the opioid concerns; however, if additional data becomes available in the future leading to additional concerns, FDA will contact Genentech to discuss further.

Should you have any additional questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Senior Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721



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

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Memorandum

**Date:** November 3, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc. (Genentech)  
*Proposed PMC Language*

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

In addition the October 30, 2015, FDA’s post-marketing requirements and post-marketing commitments proposal, please see FDA’s additional post-marketing commitment proposal. Please provide your response via email communication by noon on Thursday, November 5, 2015, or sooner if possible.

**POSTMARKETING COMMITMENTS**

**CLINICAL**

**To Further Define the Efficacy of Cobimetinib:**

1. Submit to CDRH a PMA supplement for the FDA-approved Roche cobas 4800 BRAF Mutation test, to revise the instructions for use to include an updated indications for use statement and updated clinical section to reference the detection of V600K mutations in the trial that supported the FDA approval of cobimetinib with vemurafenib for patients with unresectable or metastatic melanoma with BRAF V600E and V600K mutations.

**Submission Timeline:**

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, Structure and Content of Clinical Reports  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>.
- Guidance for Industry, entitled, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>.
- Guidance for Industry, entitled, Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
- Guidance for Industry, entitled, Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
11/03/2015



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

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Memorandum

**Date:** November 3, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** NDA 206192 – Genentech, Inc. (Genentech)  
*Proposed PMC Language*

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

In addition the October 30, 2015, FDA’s post-marketing requirements and post-marketing commitments proposal, please see FDA’s additional post-marketing commitment proposal. Please provide your response via email communication by noon on Thursday, November 5, 2015, or sooner if possible.

## **POSTMARKETING COMMITMENTS**

### **CLINICAL**

#### **To Further Define the Efficacy of Cobimetinib:**

1. Submit to CDRH a PMA supplement for the FDA-approved Roche cobas 4800 BRAF Mutation test, to revise the instructions for use to include an updated indications for use statement and updated clinical section to reference the detection of V600K mutations in the trial that supported the FDA approval of cobimetinib with vemurafenib for patients with unresectable or metastatic melanoma with BRAF V600E and V600K mutations.

#### **Submission Timeline:**

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, **Structure and Content of Clinical Reports**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>.
- Guidance for Industry, entitled, **Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>.
- Guidance for Industry, entitled, **Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
- Guidance for Industry, entitled, **Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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MEREDITH LIBEG  
11/03/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
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Memorandum

**Date:** October 30, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic (Cobimetinib).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email as soon as possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please provide the ID number for all patients who experienced serious ocular toxicity. For each event, indicate whether the event was diagnosed due to symptoms or based on routine screening in an asymptomatic patient.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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MEREDITH LIBEG  
10/30/2015



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

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Memorandum

**Date:** June 25, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

We also refer to your March 10, 2015, submission, containing a 90-day Safety Update Report; to our Advice Information Letter dated May 20, 2015, requesting additional information relating to the 90-day Safety Update; and your June 15, 2015 submission in response to the May 20, 2015 request. Based on the review of the information, our Clinical Reviewer has the following additional request for information. Please provide your response to me via email by COB on July 2, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please revised the safety data in the HIGHLIGHTS, WARNINGS and PRECAUTIONS and ADVERSE REACTIONS sections of the cobimetinib U.S. Package Insert to include data from the 90-Day Safety Update (Cut-off Date: Sept 19, 2014). The efficacy data based on the May 9, 2014, cut-off date for the primary analysis need not be updated.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
06/25/2015



NDA 206192

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) for which the first portion was submitted and received on October 30, 2014, and the final portion was submitted and received on December 11, 2014, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cobimetinib, tablet for oral use, 20 mg.

We also refer to your March 10, 2015 submission, containing a 90-day Safety Update Report and to our Advice Information Letter dated May 20, 2015, requesting additional information relating to the SDTM and ADaM datasets contained in the 90-day Safety Update. You provided a response to the May 20, 2015, letter in a June 15, 2015, amendment; we have identified this submission as a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 11, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 30, 2015.

If you have any questions, call Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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PATRICIA KEEGAN  
06/25/2015



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

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Memorandum

**Date:** May 29, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

We also refer to the clinical request for information dated May 20, 2015, and your formal response provided via email communication followed by a formal submission to the NDA on May 27, 2015, providing a proposal and requesting additional clarification to Comment 4. Furthermore, we refer to the teleconference held between Genentech and representatives of the Division of Oncology Products 2 (DOP2) on May 28, 2015, in order to aid in providing clarification. As a follow-up from the May 28, 2015, teleconference, our Clinical Reviewer has the following additional request for information. Please provide your response to me via email as soon as possible, and follow that with a formal submission to the NDA.

**Comments:**

1. In addition to the proposed analyses on the differences between the datasets from the original NDA submission and the 90 Day safety update, provide an analysis of the following:
  - Deleted AE terms, if any
  - The nature of the serious event, in addition to changes in serious events
  - Changes in concomitant medications given

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
05/29/2015



NDA 206192

## INFORMATION REQUEST

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) dated December 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Cotellic [*Proposed*] (Cobimetinib).”

We also refer to your March 10, 2015 submission, containing a 90-day Safety Update Report and to your response to FDA’s Request for Information concerning this submission, provided electronically to the FDA on May 14, 2015. Finally, we refer to the May 15, 2015, teleconference between the Division of Oncology Products 2 (DOP2) and representatives from Genentech. The purpose of the teleconference was to obtain information concerning the errors in the datasets incorrectly stating that eight patients randomized to receive vemurafenib with placebo instead received vemurafenib plus cobimetinib treatment and were analyzed in the vemurafenib plus cobimetinib group in Genentech’s safety analyses contained in the original NDA. In the 90-day Safety Update Report, Genentech now reports that seven of these patients received no cobimetinib and these patients are now included in the vemurafenib plus placebo group for the safety analyses provided in the 90-day Safety Update Report.

FDA has insufficient information to assess whether the above data errors represent a deficiency in study monitoring and auditing that would call into question the data integrity of this application. Please provide the following information as soon as possible:

1. Submit a detailed summary of the procedures followed to assure data integrity in the original NDA submission (NDA 206192, SDN 2, submitted on December 11, 2014) and in the 90-day safety update (NDA 206192, SDN 15, submitted on March 10, 2015). In your response include details of the timelines and procedures related to the preparation of the primary data submitted for FDA review (i.e., case report forms and primary source documents) including data cutoff date, data cleaning process, and database lock for the

datasets provided in the original NDA submission and for the datasets used to generate the 90-Day Safety Update.

2. Submit a discussion of the root causes, at the level of the individual study site, leading to the errors in the datasets submitted in the original NDA and the corrective measures implemented at each of the sites to address the aforementioned root causes.
3. A detailed analysis of the site monitoring reports for all study sites to identify all sites at which errors occurred with respect to randomization assignment and treatment administered.
4. Submit a comprehensive analysis of the differences between the datasets containing safety information submitted in the original NDA and those submitted in the 90-day safety update using the safety clinical data cut-off date of May 9, 2014. This analysis should include a summary of the differences between the two datasets at the patient level by treatment group and at the adverse event level by treatment group. For example, if the 90-day update AE.xpt dataset contained 100 adverse event line listings with an adverse event start date that had been revised from that recorded in the Original Submission AE.xpt dataset, provide a tabular summary that lists the total number of patients (and proportion of the safety population) and the number of patients (and proportion) by treatment arm affected by the revision. Provide a similar tabular listing based on the total number of adverse event line listings affected by the revision (total and by treatment arm).
5. Submit the SDTM and ADaM datasets and any other supporting files containing primary data summarized in the 90-Day Safety Update Report.

If you have any questions, call Meredith Libeg, Senior Regulatory Project Manager, at (301) 796-1721.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA KEEGAN  
05/20/2015



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

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Memorandum

**Date:** May 19, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

We also refer to your clinical request for information dated May 12, 2015, and your formal response provided via email communication followed by a formal submission to the NDA on May 15, 2015. Our Clinical Reviewer has the following additional request for information. Please provide your response to me via email as soon as possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please clarify whether Genentech can provide any evidence that patients with BRAF V600K mutations not detected by the cobas test would derive benefit from and would not be harmed by the combination of a BRAF-inhibitor with a MEK-inhibitor.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
05/19/2015



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

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Memorandum

**Date:** May 14, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email by Noon (PST) today, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please provide the unique subject ID numbers for the 8 patients from the GO28141 originally randomized to the Placebo arm who were identified in the original study report as having been treated with cobimetinib. For these 8 patients, provide the actual treatment status.
2. Confirm if you submitted an update safety database for the 90-Day Safety Update that occurred in March? If so, can you please point us to the location in the EDR?

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
05/14/2015



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

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Memorandum

**Date:** May 12, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email as soon as possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please provide data to support the efficacy of cobimetinib in combination with vemurafenib in patients with a low percentage of mutant BRAF V600K alleles which would be expected to be at or below the detection of the cobas test due to cross-reactivity.
2. Please review the data from the GO28141 to assess:
  - whether there is a differential use of antidepressant and narcotic use between the two study arms
  - whether there is an increase in suicidal ideation following discontinuation of cobimetinib
3. Provide a table showing the number of patients at baseline with lung mets; the number of patients at baseline with liver mets; and the number of patients at baseline with 3 or more metastatic sites by study arm (ITT) for the GO28141.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
05/12/2015



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

Memorandum

**Date:** May 6, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
**Clinical Review Comments and Information Request**

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email as soon as possible, and follow that with a formal submission to the NDA.

**Comments:**

1. The dataset CM appears to list patients reflected as having multiple second and third lines of therapies. Each patient should only have one second and one first-line therapy. Please explain and fill in the numbers for the tables below for the ITT:

Table 1. Patients receiving post-study treatment for melanoma by study arm and line of treatment – ITT study population (GO28141)

	Vem/Placebo N (%)	Vem/Cobi N (%)
Patients receiving 2nd line therapy		
Patients receiving 3rd line therapy		
Patients receiving 4th line therapy		
All patients receiving post-study treatment		

Table 2: Post-study Treatment for Melanoma. By Study Arm and type of Treatment Intent-to-Treat Population. (GO28141)

	VEM/Placebo (N=248) 45	Vem/Cobi (N=247) 39		
Second Line				
Anti PD-1				
Ipilimumab				
RAFi/MEKi				
MEKi				
RAFi				
Other investigational product				
Chemotherapy				
Third Line				
Anti PD-1				
Ipilimumab				
RAFi/MEKi				
MEKi				
RAFi				
Other investigational product				
Chemotherapy				
Fourth Line				
Chemotherapy				
Any Line				
Anti PD-1/Ipilimumab				
RAFi/MEKi, RAFi or MEKi				

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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MEREDITH LIBEG  
05/06/2015

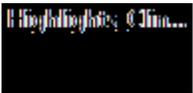
## Libeg, Meredith

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**From:** Libeg, Meredith  
**Sent:** Tuesday, May 05, 2015 4:19 PM  
**To:** 'Sarah Wayson'  
**Subject:** NDA 206192 - Genentech - Cobimetinib - FDA Request for Information (QT-IRT)

Hi Sarah

Please find attached a table from our QT-IRT group for your completion relating to your NDA application (NDA 206192) submitted on December 11, 2014. We are requesting a response to the comments and request for as soon as possible.



Should you have any questions, please don't hesitate to contact me; and kindly confirm receipt of this email.

Best regards,  
Meredith

**Meredith Libeg, P.M.P, R.A.C. (US), C.C.R.P.**

Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Phone: 301-796-1721

**Table 1. Highlights of Clinical Pharmacology and Cardiac Safety**

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/  
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MEREDITH LIBEG  
05/05/2015



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

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Memorandum

**Date:** April 3, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Pharmacology Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Pharmacology Reviewers have the following request for information. Please provide your response to me via email by COB on Wednesday, April 7, 2015, if possible, and follow that with a formal submission to the NDA.

**Comments:**

Based on your assumption of reduced intestinal first-pass metabolism of cobimetinib in cancer patients:

1. Establish an alternative PBPK model that can approximate an increased Fg of Cobimetinib. This can be accomplished by simulating cobimetinib PK using your current drug model in healthy subjects with reduced gut CYP3A content.
2. Use the alternative PBPK model to simulate the following scenarios of the effect of a moderate CYP3A inhibitor (e.g., erythromycin 500 mg three times a day [t.i.d.]) on cobimetinib exposure:
  - a. Administer cobimetinib (60 mg once daily, q.d.) and inhibitor for 21 days
  - b. Administer cobimetinib (20 mg q.d.) and inhibitor for 21 days
  - c. Administer cobimetinib (60 mg q.d.) for 21 days, initiate inhibitor dosing on day 8 for 14 days
  - d. Administer cobimetinib (60 mg q.d.) for 7 days, reduce cobimetinib dose to 20 mg q.d. and initiate inhibitor dosing on day 8 for 14 days

- e. Administer cobimetinib (60 mg q.d.) for 21 days, initiate inhibitor dosing on day 15 for 7 days
- f. Administer cobimetinib (60 mg q.d.) for 14 days, reduce cobimetinib dose to 20 mg q.d. and initiate inhibitor dosing on day 15 for 7 days
- g. Administer cobimetinib (60 mg q.d.) for 14 days, interrupt cobimetinib dosing and initiate inhibitor dosing on day 15 for 7 days

For each scenario, include simulated PK profiles of cobimetinib in the absence and in the presence of inhibitor, and summary of simulation results.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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MEREDITH LIBEG  
04/03/2015



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

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Memorandum

**Date:** April 2, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Nonclinical Review Comments and Information Request***

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Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Nonclinical Reviewers have the following request for information. Please provide your response to me via email by COB on Friday, April 3, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. In <sup>(b) (4)</sup> Study 7359-360 (13-Week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Dogs with a 4-Week Recovery), Animal H46714 (Male, Group 3) reportedly died on Study Day 1 and was replaced with another animal; however, no cause of death was assigned to the preterm decedent and no further information was provided for this animal.

Provide additional detail about the cause of death for this animal (e.g. preterminal clinical signs, veterinary and/or study-director notes).

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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MEREDITH LIBEG  
04/02/2015



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

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Memorandum

**Date:** March 25, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***QT-IRT Review Comments and Information Request***

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Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our QT-IRT Reviewers have the following request for information. Please provide your response to me via email by COB on Monday, March 30, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please submit all related ECG waveforms to the ECG warehouse at [www.ecgwarehouse.com](http://www.ecgwarehouse.com).

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
03/25/2015



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

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Memorandum

**Date:** March 25, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Pharmacology Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Pharmacology Reviewers have the following request for information. Please provide your response to me via email by COB on Wednesday, April 1, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

It appears that cobimetinib exposure is generally higher in cancer patients than in healthy subjects based on the data provided in Table 14 in your Summary of Clinical Pharmacology Studies included in the NDA.

- a. Submit your justification to support that the PBPK model developed with data from healthy subjects allows the prediction for the magnitude of cobimetinib exposure change by concomitant use of CYP3A modulators in cancer patient.
- b. Use cobimetinib and CYP3A modulator models to simulate the following scenarios in patients:
  - i. Chronic use of a moderate CYP3A inhibitor (e.g., erythromycin 500 mg three times a day [TID] starting on day 1) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.
  - ii. Short term use of a moderate CYP3A inhibitor (e.g., when cobimetinib exposure has reached steady-state, coadminister erythromycin 500 mg TID for another 14 days) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.

- iii. Chronic use of a moderate CYP3A inducer (e.g., efavirenz 600 mg once daily [QD] starting on day 1) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.
  - iv. Short term use of a moderate CYP3A inducer (e.g., when cobimetinib exposure has reached steady-state, coadminister efavirenz 600 mg QD for another 14 days) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.
- c. Provide the model files used to generate the final PBPK simulations (e.g., drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Submit software specific excel files such as parameter estimation data files and simulation outputs as MS Excel files. Provide study report(s) as PDF files (incorporate screenshots if required).

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
03/25/2015



NDA 206192

**METHODS VALIDATION  
MATERIALS RECEIVED**

Genentech  
Attention: Lal Ninan, Ph.D.  
1 DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Lal Ninan, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for 20 mg Cobimetinib and to our February 23, 2015 letter requesting sample materials for methods validation testing.

We acknowledge receipt on March 24, 2015, 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 (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Laura C. Pogue  
MVP Coordinator (alternate)  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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LAURA POGUE  
03/24/2015



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

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Memorandum

**Date:** March 17, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Reviewers have the following request for information. Please provide your response to me via email by COB on Thursday, March 19, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please indicate if the following risk factors were captured in the database:
  - Assessment of prior sun damage/exposure either in history of blistering sunburns or systematic dermatological assessment of chronic sun damaged skin.
  - Location of the primary melanoma. Can they pull out patients with a primary on the head/neck?

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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MEREDITH LIBEG  
03/17/2015



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

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Memorandum

**Date:** March 6, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Statistical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Statistical Reviewers have the following request for information. Please provide your response to me via email by COB on Friday, March 13, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Please confirm variables 'REGION' and 'METASTAT' in analysis datasets adsl.xpt and adte.xpt recorded the data from case report form (CRF). Please confirm that variable 'STAGIVRS' in analysis dataset adsl.xpt recorded the data of the stratified factor Metastatic Classification from IVRS. Please provide direction of how to locate the variables that recorded the 'region' data from IVRS.
2. Per the statistical analysis plan (SAP) of Study GO28141, a PFS sensitivity analysis 'PFS censoring accounting for missed visits' would be conducted. Please provide direction of how to locate this sensitivity analysis result and the analysis dataset that can be used to reproduce the result if they were already provided on December 11, 2014, NDA submission. If not, please provide the sensitivity analysis result and the dataset. Please include a variable into the submitted analysis dataset that indicate the patients who were censored at the date of the last evaluable tumor assessment due to die or progress after two or more consecutive missed visits.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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MEREDITH LIBEG  
03/06/2015



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

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Memorandum

**Date:** March 6, 2015

**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2

**Subject:** **NDA 206192** – Genentech, Inc.  
***Chemistry, Manufacturing, and Controls (CMC) Review Comments and  
Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our CMC Reviewers have the following request for information. Please provide your response to me via email by COB on Friday, March 13, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. The description of your product in section 3.2.P.1 states that the tablets will be debossed with "COB" on one side. However, the tablet compression operation in the executed batch records show (b) (4) was embossed on one side. Please clarify if your tablets are debossed or embossed and explain if the difference would impact the drug product quality.
2. You have not provided information for the individual packaging process of the drug products in bottles.
  - a. Provide individual packaging process of the drug products in bottles in the manufacturing flow chart, description of the manufacturing process and process controls.
  - b. Update Master Batch Records and Executed Batch Records with the information of the individual packaging process.

3. You proposed an in-process test for the individual core tablet weight. Include a test for the average weight of the core tablets with an acceptable criterion at (b) (4) % of the target value.
4. Your proposal for the acceptance criterion of the core tablet hardness at NLT (b) (4) is not justified by the drug product quality (e.g. core tablet appearance). As shown in your (b) (4) test results, the core tablet appearance (b) (4) are dramatically improved when hardness (b) (4). Increase the acceptance criterion for the core tablet hardness accordingly or justify the current control of the hardness is adequate based on meeting the product's QTPP and resulting CQAs including tablet appearance and integrity. Additionally, consider including (b) (4) (b) (4) for better assurance of tablet integrity.
5. You proposed a drug product specification with a Microbial Limits testing for the first and last batch of each drug product campaign. Skip-lot testing for drug products is not allowed per 21 CFR 211.165 (a) and (b). If a drug product specification includes testing for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the drug product specification at release provided adequate (b) (4) microbiological controls are established and documented. If you wish to omit the microbial limits at drug product release, please provide the following:
  - a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
  - b. Describe microbiological monitoring and acceptance criteria for the critical control points (b) (4) that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
  - c. Describe activities taken when microbiological acceptance criteria are not met at control points.
  - d. You should minimally perform microbial limits testing at the initial stability testing time point. Testing must be performed on every lot of drug product produced.

Please submit a revised drug product specification for whichever microbial limits testing alternative that you select.

6. The (b) (4) drug substance have significantly different solubility that could impact the safety or efficacy profile of your product. Provide a study summary on the potential formation of the drug substance (b) (4) in drug product. Based on the likelihood (b) (4) drug substance formation in the drug product, comment on the impact to the patient.
7. (b) (4) can impact the drug product's (b) (4) dissolution. Data in 3.2.P.8 shows that dissolution slows on stability. Add a test and the acceptance criterion for (b) (4) drug product specification.

8. Explain your decision to use long-term storage conditions for drug product stability test at 30°C/75% RH. Per ICH Q1A, the long-term storage condition for drug product stability test should be at 25°C/60% RH or 30°C/65% RH.
9. Provide additional post-approval stability commitments to continue stability studies on the primary batches and the batches packaged at the commercial packaging site (Roche, Segrate, Italy) through the completion of your stability protocol to generate the real time data for the proposed shelf life.
10. In your submission, solubility and permeability data are presented to support your statement that cobimetinib hemifumarate's in vivo absorption/pharmacokinetic characteristics are consistent with (b)(4). If you intend to have your drug substance and drug product officially classified as a (b)(4) by FDA, submit this request under your IND.
11. All comparative data presented in Sections 2.3.3.3 and 2.3.3.4 of 3.2.P.2 Pharmaceutical Development to support the discriminating power of your proposed dissolution method lacks a description of the batches used to develop and validate your dissolution method. The discriminating power of the method is best exemplified using the target commercial batch as the basis for comparison.
  - a. Please justify the choice of batches used in Sections 2.3.3.3 and 2.3.3.4 and explain how inferences of dissolution method robustness and discriminating power can be extrapolated to the proposed commercial batches.
  - b. Please provide a side-by-side comparison of the qualitative and quantitative composition of the 20 and (b)(4) mg strengths, highlighting (where relevant) the differences (expressed as %w/w). This comparison should include batches 73457-94, PT9754 B01, and PT2338 B01.
  - c. In Section 3.2.P.2. (Pharmaceutical Development), Table P.2-32 shows the dissolution method testing matrix for the 20 mg and (b)(4) mg film-coated tablets. You state that individual and mean dissolution results for both strengths were similar, but no data are presented to support this assertion. Provide clearly labeled and tabulated data for all test conditions graphically presented in section 2.3.3 of the Pharmaceutical Development report. Include individual, mean, minimum, maximum and standard deviation values and ensure that the data are in XPT, as well as PDF formats in your response.
12. In 3.2.P.5.1 Specifications, your proposed acceptance criterion for in vitro dissolution is Q (b)(4)% at 20 minutes based on S1, S2 or S3. The data submitted in section 3.2.P.8.3 Stability Data appear to support an earlier specification time point. Please submit a proposal for a revised acceptance criterion or justify the acceptance criteria at 20 minutes.

13. Submit the individual vessel dissolution data for the clinical and registration batches at release, zero stability time point (Initial Analysis), and throughout the stability program. Provide the individual vessel dissolution results in editable XPT format using the following long/stacked layout:

Storage Condition	Batch	Vessel	Time	% Release
At Release	PT2338 B03	1	5	xx
At Release	PT2338 B03	1	10	xx
At Release	PT2338 B03	1	15	xx
At Release	PT2338 B03	1	20	xx
At Release	PT2338 B03	1	45	xx
At Release	PT2338 B03	1	60	xx
At Release	PT2338 B03	2	5	xx
etc..				
At Release	PT2338 B03	2	60	xx
etc..				
At Release	PT2338 B03	12	60	xx
Initial Analysis	PT2338 B03	1	10	xx
Initial Analysis	PT2338 B03	1	15	xx
Initial Analysis	PT2338 B03	1	20	xx
Initial Analysis	PT2338 B03	1	45	xx
Initial Analysis	PT2338 B03	1	60	xx
Initial Analysis	PT2338 B03	2	5	xx
etc..				
Initial Analysis	PT2338 B03	2	60	xx
etc..				
Initial Analysis	PT2338 B03	12	60	xx
30C/75RH 1 Month	PT2338 B03	1	5	xx
etc..				
30C/75RH 1 Month	PT2338 B03	6	60	xx
etc..				
40C/75RH 6 Month	PT2338 B03	6	60	xx
Initial Analysis	<b>PT2338 B04</b>	1	5	xx
etc..				
40C/75RH 6 Month	<b>PT2338 B04</b>	6	60	xx
<b>etc..</b>				

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
03/06/2015



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

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Memorandum

**Date:** February 27, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email by COB on Monday, March 2, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. There appear to be no patients in the ADSL for GO28141 with a value of Y for the variable DISCAE and STDDRS does not appear to have a value for patients withdrawn from study due to an adverse event. If a patient has a value of Y for DISCMEC and a value of Y for DISCVEM and “ADVERSE EVENT” for both MEKDRS and VEMDRS, does this indicate that the drug was permanently discontinued due to an adverse event? Should such patients be considered withdrawn from study due to an adverse event.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
02/27/2015



NDA 206192

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Genentech  
Attention: Lal Ninan, Ph.D.  
1 DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Lal Ninan, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for 20 mg Cobimetinib.

We will be performing methods validation studies on 20 mg Cobimetinib, as described in NDA 206192.

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

**Method, current version**

- 3.2.S.4.2.3 Identity, Assay, and Organic Impurities of Cobimetinib Drug Substance by HPLC
- 3.2.S.4.2.8 Determination of (b) (4) by Gas Chromatography
- 3.2.P.5.2.4 Identity, Assay, and Degradation Products by HPLC
- 3.2.P.5.2.5 Uniformity of Dosage Units by Content Uniformity by HPLC
- 3.2.P.5.2.6 Dissolution

**Samples and Reference Standards**

- 2 (b) (4) g of Cobimetinib drug substance
- 2 (b) (4) mg of Cobimetinib reference standard
- 1 (b) (4) g bottle of (b) (4)
- 200 20 mg Cobimetinib Tablets
- 1 (b) (4) mg each for the following impurities: (b) (4)

**Equipment**

1  
1  
  
1  
1  
50

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: MVP Sample Custodian  
645 S Newstead  
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (laura.pogue@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Laura C. Pogue, Ph.D.  
MVP coordinator (alternate)  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
02/23/2015



NDA 206192

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) for which the first portion was submitted and received on October 30, 2014, and the final portion was submitted and received on December 11, 2014, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cobimetinib, tablet for oral use, 20 mg.

We also refer to your submissions dated October 30, 2014, December 11, 2014, December 19, 2014, December 23, 2014, January 6, 2015, January 8, 2015 (2), February 2, 2015, February 4, 2015, February 6, 2015, February 10, 2015, and February 14, 2015 (2). Lastly, we refer to our communication of February 13, 2015, informing you that the review classification for this application is Priority and potential review issues would be forthcoming.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Revise the proposed prescribing information to replace the [TRADENAME] to the proposed proprietary name [COTELLIC] throughout the document as appropriate.

2. Revise Section 5.1 “Serious Retinopathy” to remove the reference to (b) (4) Cross-referenced information in product labeling should be indicated as follows: “[see *Dosage and Administration* (2.2)].”
3. Revise Section 5.2 “Left Ventricular Dysfunction” to remove the reference to (b) (4) Cross referenced information in labeling should be indicated as follows: “[see *Dosage and Administration* (2.2)].”
4. Revise Section 6.1 “Clinical Trials Experience” to include the following verbatim statement:  
“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”
5. Revise Section 8 “USE IN SPECIFIC POPULATIONS” to reflect the draft Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry (December 2014) found at:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>.
6. Clinical requests for revisions to the labeling are embedded in the attached document.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by Friday, March 20, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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), and patient PI. 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), and patient PI, 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(s) 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 Meredith Libeg, Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ATTACHMENTS: FDA Proposed Labeling Revisions

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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PATRICIA KEEGAN  
02/23/2015



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

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Memorandum

**Date:** February 13, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email as soon as possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Clarify which variable in the ADAE data set codes for the MedDRA PT.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
02/13/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206192

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Genentech, Inc.  
1 DNA Way, MS241A  
South San Francisco, CA 94080

ATTENTION: Sarah Wayson, Ph.D.  
Regulatory Program Management

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) dated December 11, 2014, received December 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cobimetinib Tablets, 20 mg.

We also refer to your January 6, 2015, correspondence, received January 6, 2015, requesting review of your proposed proprietary name, Cotellic.

We have completed our review of the proposed proprietary name, Cotellic, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your January 6, 2015, 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 Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Meredith Libeg, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1721.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy 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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LUBNA A MERCHANT on behalf of TODD D BRIDGES  
02/13/2015



NDA 206192

**PRIORITY REVIEW DESIGNATION**

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) for which the first portion was submitted and received on October 30, 2014, and the final portion was submitted and received on December 11, 2014, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cobimetinib, tablet for oral use, 20 mg.

We also refer to your submissions dated October 30, 2014, December 11, 2014, December 19, 2014, December 23, 2014, January 6, 2015, January 8, 2015 (2), February 2, 2015, February 4, 2015, and February 6, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is August 11, 2015.

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, mid-cycle, 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 requirement/commitment requests by July 1, 2015.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before February 23, 2015.

If you have any questions, call Meredith Libeg, Regulatory Project Manager, at (301) 796-1721.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA KEEGAN  
02/13/2015



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

**Memorandum**

**DATE:** February 12, 2015

**FROM:** Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

**SUBJECT:** Review Designation memo

Sponsor: Genentech, Inc.  
Product: Cotellic (cobimetinib), 20 mg tablets  
Proposed Indication: For use in combination with Zelboraf®  
(vemurafenib) for the treatment of patients with  
unresectable or metastatic melanoma with BRAF  
V600 mutation

**TO:** NDA 206192

The review status of this file submitted as a New Molecular Entity (NME) NDA is designated to be:

Standard (PDUFA V - 12 Months)

Priority (PDUFA V - 8 Months)

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**BACKGROUND**

Genentech is requesting priority review based on the potential to address an unmet medical need. Genentech based their request on the following:

While the therapeutic options have improved significantly in recent years for patients with BRAF-mutated melanoma, there is still significant disease-related

mortality. As a result, an ongoing need exists for drugs or drug combinations with acceptable safety profiles that can further improve clinical outcomes.

Although the advent of immune-directed and targeted therapy has positively impacted the initial management for metastatic melanoma, each class of agent has unique limitations (see [NCCN Guidelines for physicians on treatment of melanoma, 2014](#)). For immunotherapy, the potential exists for serious immune-mediated toxicity, responses may take months to become apparent and response rates are typically < 25% (see [Appendix 1](#)).

Despite the clear clinical benefit associated with BRAF- and MEK-directed therapies, the onset of drug-resistant disease coupled with a lack of effective post-progression therapies mean that many patients with BRAF-mutated melanoma will succumb to their disease, usually within 2 years ([Chapman et al. 2011](#); [Sosman et al. 2012](#); [McArthur et al. 2014](#); [Flaherty et al. 2012](#); [Hauschild et al. 2012](#)). In the first-line setting, additional drugs or drug combinations are needed to combat BRAF inhibitor resistance in order to improve the durability of responses.

Study GO28141 is a multicenter, randomized, double-blind, placebo-controlled, Phase III study designed to evaluate the safety and efficacy of cobimetinib in combination with vemurafenib as compared to vemurafenib alone, in patients with BRAF V600 mutation positive advanced melanoma. Cobimetinib plus vemurafenib treatment resulted in a statistically significant and clinically meaningful increase in investigator-assessed PFS, compared with placebo plus vemurafenib. The median PFS was 9.9 months (95% CI: 9.0, upper bound not reached) in the cobimetinib plus vemurafenib arm and 6.2 months (95% CI: 5.6, 7.4 months) in the placebo plus vemurafenib arm. The stratified Hazard Ratio (HR) for investigator-assessed PFS was 0.51 (95% CI: 0.39, 0.68; log-rank  $p < 0.0001$ ) in favor of the cobimetinib plus vemurafenib arm, corresponding to a 49% reduction in the risk of disease progression or death in favor of the combination of cobimetinib and vemurafenib.

A clear treatment effect was observed in all secondary measures of efficacy evaluated amongst patients treated with cobimetinib and vemurafenib including PFS as assessed by independent review and overall response rate. The median PFS by independent review was 11.3 months (95% CI: 8.5, upper bound not reached) in the cobimetinib plus vemurafenib arm and 6.0 months (HR 0.60; 95% CI: 5.6, 7.5). The ORR as determined by the investigator was statistically significantly higher in the cobimetinib plus vemurafenib arm (67.6%, 95% CI: 61.4, 73.4) than in the placebo plus vemurafenib arm (44.8%, 95% CI: 38.5, 51.2,  $p < 0.0001$ ), including complete response in 10.1% of patients in the cobimetinib plus vemurafenib arm and 4.4% of patients in the placebo plus vemurafenib arm.

## **ASSESSMENT OF REQUEST**

In evaluating Genentech's request for priority review designation, I considered their rationale including the summary results of the Study GO28141 and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

**Assessment:**

This New Drug Application (NDA) was not submitted under the statutory provisions for which priority review designation is required by statute.

An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. Unresectable or metastatic melanoma with BRAF V600 mutation is a serious condition, with a median survival of less than 18 months, as demonstrated by clinical trial supporting the approval of vemurafenib. Therefore, this condition would be considered to have an unmet medical need.

Available therapy for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation include

- vemurafenib
- dabrafenib
- ipilimumab
- trametinib

**Vemurafenib** received approval on August 17, 2011, for the treatment of patients with unresectable or metastatic melanoma with BRAF-V600E mutation as detected by an FDA-approved test. Vemurafenib is not recommended for use in patients with wild-type BRAF melanoma. This approval was based on demonstration of a clinically important and statistically significant improvement in overall survival as compared to dacarbazine; based on updated results, the median overall survival was 13.6 months vs 10.3 months for vemurafenib and dacarbazine, respectively. This was supported by demonstration of improvements in progression-free survival (5.3 vs. 1.6 months) and overall response rates (48.4% vs. 5.5%).

**Ipilimumab** received approval on March 25, 2011, for the treatment of unresectable or metastatic melanoma. This approval was based on demonstration of a clinically important and statistically significant improvement in overall survival as compared to an investigational vaccine, with median survivals of 10 months for ipilimumab vs. 6 months for the investigational vaccine. These results were supported by demonstration of improved survival in a second trial comparing ipilimumab with dacarbazine.

**Dabrafenib** received traditional approval on May 29, 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations, as detected by an FDA-approved test. Dabrafenib is not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy. This approval was based on demonstration of a clinically important improvement in progression-free survival as compared to dacarbazine, with a median PFS of 5.1 months and 2.7 months for dabrafenib and dacarbazine, respectively, and supported by improvement in overall response rates (52% vs. 17%).

**Trametinib** received traditional approval on May 29, 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or BRAF V600K mutations, as detected by an FDA-approved test. Trametinib is not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy. This approval was

based on demonstration of a clinically important improvement in progression-free survival as compared to chemotherapy (dacarbazine or paclitaxel) with a median PFS of 4.8 months in the trametinib arm as compared to 1.5 months in the chemotherapy arm.

**Other approved drugs:** There are additional drugs which are approved for a broader population of patients with unresectable or metastatic melanoma (i.e., regardless of BRAF mutation status), which include pembrolizumab, nivolumab, aldesleukin, dacarbazine, and hydroxyurea. In addition, there are two drugs approved in combination for treatment of patients with BRAF mutation-positive melanoma. These other drugs are not considered “available therapy” for the following reasons:

- Dacarbazine and hydroxyurea are no longer relevant to the US standard of care for this patient population.
- Aldesleukin is indicated only for patients with excellent performance status and end-organ function; it is administered at high doses requiring intensive cardiopulmonary monitoring and support. Therefore its use is limited to the specialized medical centers and thus is not considered part of the US standard of care at most institutions.
- Pembrolizumab, as a single agent, and nivolumab, as a single agent, were approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) based on demonstration of an effect on a surrogate endpoint (durable responses) and therefore are not considered available therapy.
- Dabrafenib and trametinib for use in combination were approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) based on demonstration of an effect on a surrogate endpoint (durable responses) and therefore are not considered available therapy.

### **Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition**

Based on the results summarized above for Study GO28141, the addition of cobimetinib to vemurafenib provides a clinically important improvement in progression-free survival over vemurafenib alone. These results provide “evidence of increased effectiveness in treatment, of a condition” over the available therapy of vemurafenib.

It is noted that the trial did not compare the effects of cobimetinib to all available therapy. There are multiple agents approved for the initial treatment of unresectable or metastatic melanoma, including ipilimumab that is approved for a population includes those with both BRAF V600 mutations and patients without such mutations. However, the selection of the comparator (vemurafenib alone) in Study GO28141 is reasonable and supported by the NCCN practice guidelines, summarized below.

*The choice of initial therapy in patients with melanoma should be guided by the “BRAF mutation status, tempo of the disease, and presence or absence of cancer-related symptoms. Patients with low volume, asymptomatic, metastatic melanoma may be good candidates for immunotherapy (ipilimumab or IL-2), as there may be time for a durable anti-tumor response to emerge. Patients who have BRAF-mutant melanoma who have symptomatic disease or who have progressed despite immunotherapy should be*

*considered for targeted therapies. Clinical trials are underway to address unanswered questions regarding the optimal sequencing and/or combinations of these agents.*

*Vemurafenib, dabrafenib, and trametinib are recommended only for patients with documented BRAF V600 mutations. The panel preferred BRAF inhibition or combined BRAF/MEK inhibition over trametinib monotherapy and did not recommend trametinib monotherapy for patients who progressed from previous treatment with BRAF inhibitors. Trametinib monotherapy can be used in patients who show intolerance to toxicities related to vemurafenib or dabrafenib”.*

Based on demonstration of a clinically important improvement in progression-free survival [HR 0.51 (95% CI: 0.39, 0.68) corresponding to median PFS of 9.9 months vs. 6.2 months] with the addition of cobimetinib to vemurafenib over vemurafenib alone, in a serious condition with an unmet medical need, I concur with Genentech’s request for priority review designation.

**Recommendation:** Priority review

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA KEEGAN  
02/13/2015



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

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Memorandum

**Date:** February 11, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Office of Scientific Investigations (OSI) Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our OSI Reviewer has the following request for information. Please provide your response to me via email Friday, February 13, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. In the BIMO Reviewers Guide, you provided the following information regarding OSI Part II, “Request for Subject Level Data Listings by Site”:

II. Request for Subject Level Data Listings by Site

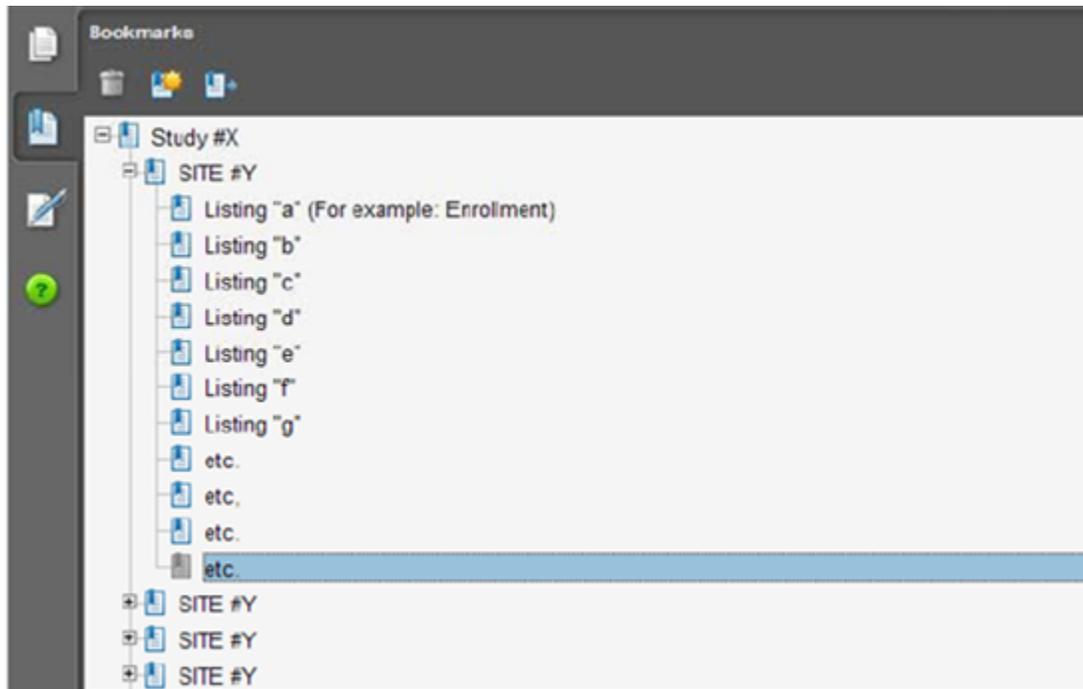
The following subject level data listings, for a total of 9 listings, are provided. There were a total of 161 sites for GO28141 and 10 sites for NO25395. One PDF file is provided for each study:

- Listing 1: Subjects Enrolled
- Listing 2: Subject Treatment Assignment
- Listing 3: Subject Discontinuation
- Listing 4: Protocol Violations and/or Deviations
- Listing 5: Subject Eligibility
- Listing 6: Adverse Events, Serious Adverse Events, and Death
- Listing 8: Primary and Secondary Endpoint Parameters
- Listing 9: Concomitant Medications
- Listing 10: Testing Performed for Safety Monitoring

Under Section 5.3.5.4, GO28141: Data listings, we note the existence of SAS files/data listing; however, OSI is not able to use these files. Additionally, we cannot locate the listing in a PDF and bookmarked file for each site. As a result, can you please provide the following or alternatively, provide the location in the submission where this information can be located:

## Part II. Request for Subject Level Data Listings by Site

- I. For study GO28141: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate)
  - j. By subject listing, of protocol-specified testing (e.g., laboratory, ECG) performed for entry criteria and safety monitoring throughout the study
  
- II. We require that one PDF file be created for study GO28141 using the following format:



If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
02/11/2015



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

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Memorandum

**Date:** February 4, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Pharmacology Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Pharmacology Reviewer has the following request for information. Please provide your response to me via email Tuesday, February 17, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

Based on initial review of the PBPK study report “Assessment of Drug-Drug Interaction Potential between Cobimetinib and CYP3A4 Inhibitors/Inducers using a Physiologically-Based Pharmacokinetic (PBPK) Approach,” please address the following:

1. You used clinical DDI data with itraconazole (Study GP28620) and sensitivity analysis to inform  $f_{m,CYP3A}$  of the cobimetinib model.
  - a. Besides simulation of exposure ratios, provide simulated  $C_{max}$ , AUC, and  $F_g$  of cobimetinib after oral administration (Study MEK4952g and no-inhibitor arm of Study GP28620) under different  $f_m$  values and  $Q_{gut}$  values used in Table 2.
  - b. Provide  $f_{m,CYP3A}$  based on in vitro data.
2. Update your simulation of the effect of rifampin on the exposure of cobimetinib using a modified rifampin PBPK model according to SimCYP’s recent update with regard to induction potency.

3. Provide the model files used to generate the final PBPK simulations (e.g., drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
02/04/2015



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

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Memorandum

**Date:** February 4, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
*Pharmacovigilance Review Comments and Information Request*

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Pharmacovigilance Reviewer has the following request for information. Please provide your response to me via email Friday, February 6, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with cobimetinib following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005) (Attached). If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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# Guidance for Industry

## Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**March 2005  
Clinical Medical**

# Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

*Additional copies are available from:  
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*<http://www.fda.gov/cder/guidance/index.htm>  
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Manufacturers Assistance, HFM-40  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike, Rockville, MD 20852-1448  
<http://www.fda.gov/cber/guidelines.htm>.*

*(Tel) Voice Information System at 800-835-4709 or 301-827-1800*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
March 2005  
Clinical Medical**

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# Guidance for Industry<sup>1</sup>

## Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

### I. INTRODUCTION

This document provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components).<sup>2</sup> Specifically, this document provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

### II. BACKGROUND

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<sup>1</sup> This guidance has been prepared by the PDUFA III Pharmacovigilance Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

<sup>2</sup> For ease of reference, this guidance uses the term *product* or *drug* to refer to all products (excluding blood and blood components) regulated by CDER and CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.

**Paperwork Reduction Act Public Burden Statement:** This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0001 (until March 31, 2005) and 0910-0338 (until August 31, 2005).

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### **A. PDUFA III's Risk Management Guidance Goal**

On June 12, 2002, Congress reauthorized, for the second time, the Prescription Drug User Fee Act (PDUFA III). In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting premarketing risk assessment, (2) developing and implementing risk minimization tools, and (3) performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9 – 11, 2003, to discuss the concept papers. FDA considered all of the comments received in developing three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

1. *Premarketing Risk Assessment (Premarketing Guidance)*
2. *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*
3. *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*

### **B. Overview of the Risk Management Guidances**

Like the concept papers and draft guidances that preceded them, each of the three final guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on premarketing and postmarketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

- Many recommendations in this guidance are ***not*** intended to be generally applicable to all products.

Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (see e.g., FDA requirements for professional labeling, and adverse

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event monitoring and reporting). As a result, many of the recommendations presented here focus on situations when a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for all products or only this subset of products.

- It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy.<sup>3</sup>

- To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as appropriate.

The topics covered in this guidance are being discussed in a variety of international forums. We are participating in these discussions and believe that, to the extent possible, the recommendations in this guidance reflect current thinking on related issues.

- When planning risk assessment and risk minimization activities, sponsors should consider input from health care participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and third party payers).
- There are points of overlap among the three guidances.

We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

### **III. THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT**

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

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<sup>3</sup> See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to FDA (45 CFR 164.512(b)(1)(i) and (iii), and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see <http://www.hhs.gov/ocr/hipaa>.

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This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term *pharmacovigilance* to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.

Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

#### **IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES**

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

##### **A. Good Reporting Practice**

Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events,<sup>4</sup> and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer, it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

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<sup>4</sup> Good reporting practices are extensively addressed in a proposed FDA regulation and guidance documents. See (1) Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, 68 FR 12406 (March 14, 2003), (2) FDA guidance for industry on *Postmarketing Reporting of Adverse Experiences*, (3) FDA guidance for industry on *E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR)*, (4) FDA guidance for industry on *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

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FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

### **B. Characteristics of a Good Case Report**

Good case reports include the following elements:

1. Description of the adverse events or disease experience, including time to onset of signs or symptoms;
2. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;
3. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;
4. Documentation of the diagnosis of the events, including methods used to make the diagnosis;
5. Clinical course of the event and patient outcomes (e.g., hospitalization or death);<sup>5</sup>
6. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;
7. Information about response to dechallenge and rechallenge; and
8. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, good case reports also include full descriptions of the following, when such information is available:

1. Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container);
2. Sequence of events leading up to the error;
3. Work environment in which the error occurred; and
4. Types of personnel involved with the error, type(s) of error, and contributing factors.

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<sup>5</sup> Patient outcomes may not be available at the time of initial reporting. In these cases, follow-up reports can convey important information about the course of the event and serious outcomes, such as hospitalization or death.

## *Contains Nonbinding Recommendations*

FDA recommends that sponsors capture in the case narrative section of a medication error report all appropriate information outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy.<sup>6</sup> Although sponsors are not required to use the taxonomy, FDA has found the taxonomy to be a useful tool to categorize and analyze reports of medication errors. It provides a standard language and structure for medication error-related data collected through reports.

### **C. Developing a Case Series**

FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS) or Vaccine Adverse Events Reporting System (VAERS), using thorough database search strategies based on updated coding terminology (e.g., the Medical Dictionary for Regulatory Activities (MedDRA)). When available, FDA recommends that standardized case definitions (i.e., formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series.<sup>7</sup> In general, FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation (see section IV.F. for more details).

As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

1. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
2. Absence of symptoms related to the event prior to exposure;
3. Evidence of positive dechallenge or positive rechallenge;
4. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
5. Consistency of the event with the known effects of other products in the class;

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<sup>6</sup> See <http://www.nccmerp.org> for the definition of a medication error and taxonomy of medication errors.

<sup>7</sup> See, for example, Institute of Medicine (IOM) Immunization Safety Review on Vaccines and Autism, 2004.

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6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and
7. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA does not recommend any specific categorization of causality, but the categories *probable*, *possible*, or *unlikely* have been used previously.<sup>8</sup> If a causality assessment is undertaken, FDA suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. A number of references are available to assist sponsors in capturing a complete account of the event.<sup>9</sup> FDA recommends that sponsors follow up to the extent possible with reporters to capture a complete account of the event, focusing on the *medication use systems* (e.g., prescribing/order process, dispensing process, administration process). This data may be informative in developing strategies to minimize future errors.

### **D. Summary Descriptive Analysis of a Case Series**

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

1. The clinical and laboratory manifestations and course of the event;

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<sup>8</sup> See World Health Organization, the Uppsala Monitoring Center, 2000, *Safety Monitoring of Medicinal Product*, for additional categorizations of causality.

<sup>9</sup> See Cohen MR (ed), 1999, *Medication Errors*, American Pharmaceutical Association, Washington DC; Cousins DD (ed), 1998, *Medication Use: A Systems Approach to Reducing Errors*, Joint Commission on Accreditation of Healthcare Organizations, Oakbrook Terrace, IL.

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2. Demographic characteristics of patients with events (e.g., age, gender, race);
3. Exposure duration;
4. Time from initiation of product exposure to the adverse event;
5. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;
6. Use of concomitant medications;
7. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;
8. The route of administration (e.g., oral vs. parenteral);
9. Lot numbers, if available, for products used in patients with events; and
10. Changes in event reporting rate over calendar time or product life cycle.

#### **E. Use of Data Mining to Identify Product-Event Combinations**

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or so-called *data mining*, can provide additional information about the existence of an excess of adverse events reported for a product. By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product-event combinations warranting further investigation. Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the "observed reporting fraction") with (2) the fraction of reports for the same particular event for all drugs (i.e., "the expected reporting fraction").<sup>10</sup> This analysis can be refined by adjusting for aspects of reporting (e.g., the reporting year) or characteristics of the patient (e.g., age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease.

The score (or statistic) generated by data mining quantifies the disproportionality between the observed and expected values for a given product-event combination. This score is compared to a threshold that is chosen by the analyst. A potential excess of adverse events is operationally defined as any product-event combination with a score exceeding the specified threshold. When

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<sup>10</sup> Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

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applying data mining to large databases (such as AERS), it is not unusual for a product to have several product-event combinations with scores above a specified threshold. The lower the threshold, the greater the likelihood that more combinations will exceed the threshold and will warrant further investigation.

Several data mining methods have been described and may be worth considering, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm<sup>11,12</sup>, the Proportional Reporting Ratio (PRR) method<sup>13,14</sup> and the Neural Network approach.<sup>15</sup> Except when the observed number of cases with the drug event combination is small (e.g., less than 20) or the expected number of cases with the drug event combination is  $< 1$ , the MGPS and PRR methods will generally identify similar drug event combinations for further investigation.<sup>16</sup>

Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products. FDA exercises caution when making such comparisons, because voluntary adverse event reporting systems such as AERS or VAERS are subject to a variety of reporting biases (e.g., some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other comorbidities or unrecorded confounders, may cause the events to be reported). In addition, AERS or VAERS data may be affected by the submission of incomplete or duplicate reports, under-reporting, or reporting stimulated by publicity or litigation. As reporting biases may differ by product and change over time, and could change differently for different events, it is not possible to predict their impact on data mining scores.

Use of data mining techniques is not a required part of signal identification or evaluation. If data mining results are submitted to FDA, they should be presented in the larger appropriate clinical epidemiological context. This should include (1) a description of the database used, (2) a description of the data mining tool used (e.g., statistical algorithm, and the drugs, events and

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<sup>11</sup> DuMouchel W and Pregibon D, 2001, Empirical Bayes screening for multi-item associations, *Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining*.

<sup>12</sup> Szarfman A, Machado SG, and O'Neill RT, 2002, Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database, *Drug Safety* 25(6): 381-92.

<sup>13</sup> Evans SJW, Waller P, and Davis S, 1998, Proportional reporting ratios: the uses of epidemiological methods for signal generation [abstract], *Pharmacoepidemiology and Drug Safety* 7:S102.

<sup>14</sup> Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

<sup>15</sup> Bate A et al., 1998, A Bayesian neural network method for adverse drug reaction signal generation, *European Journal of Clinical Pharmacology* 54:315-21.

<sup>16</sup> This conclusion is based on the experience of FDA and of William DuMouchel, Ph.D., Chief Scientist, Lincoln Technologies, Wellsley, MA, as summarized in an email communication from Dr. DuMouchel to Ana Szarfman, M.D., Ph.D., Medical Officer, OPaSS, CDER, on October 13, 2004.

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stratifications selected for the analyses) or an appropriate reference, and (3) a careful assessment of individual case reports and any other relevant safety information related to the particular drug-event combination of interest (e.g., results from preclinical, clinical, pharmacoepidemiologic, or other available studies).

### **F. Safety Signals That May Warrant Further Investigation**

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, numbers treated, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

1. New unlabeled adverse events, especially if serious;
2. An apparent increase in the severity of a labeled event;
3. Occurrence of serious events thought to be extremely rare in the general population;
4. New product-product, product-device, product-food, or product-dietary supplement interactions;
5. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);
6. Confusion about a product's name, labeling, packaging, or use;
7. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);
8. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal);<sup>17</sup> and
9. Other concerns identified by the sponsor or FDA.

### **G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates**

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment.

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<sup>17</sup> For a detailed discussion of risk minimization action plan evaluation, please consult the *RiskMAP Guidance*.

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In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate. Limitations in national denominator estimates arise because:

1. Accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available;
2. It may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low;<sup>18</sup> and
3. A product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator.<sup>19,20</sup> FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes.

To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). These background rates can be derived from: (1) national health statistics, (2) published medical literature, or (3) ad hoc studies, particularly of

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<sup>18</sup> See *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group V, Geneva, 2001.

<sup>19</sup> See Rodriguez EM, Staffa JA, Graham DJ, 2001, *The role of databases in drug postmarketing surveillance*, *Pharmacoepidemiology and Drug Safety*, 10:407-10.

<sup>20</sup> In addition to U.S. reporting rates, sponsors can provide global reporting rates, when relevant.

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subpopulations, using large automated databases or ongoing epidemiologic investigations with primary data collection. FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria, and duration of time at risk.

While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g., publicity, newness of product to the market) and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

### **V. BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES**

FDA recognizes that there are a variety of methods for investigating a safety signal. Signals warranting additional investigation can be further evaluated through carefully designed non-randomized observational studies of the product's use in the "real world" and randomized trials. The *Premarketing Guidance* discusses a number of types of randomized trials, including the large simple safety study, which is a risk assessment method that could be used either pre- or post-approval.

This document focuses on three types of non-randomized observational studies: (1) pharmacoepidemiologic studies, (2) registries, and (3) surveys. By focusing this guidance on certain risk assessment methods, we do not intend to advocate the use of these approaches over others. FDA encourages sponsors to consider all methods to evaluate a particular safety signal. FDA recommends that sponsors choose the method best suited to the particular signal and research question of interest. Sponsors planning to evaluate a safety signal are encouraged to communicate with FDA as their plans progress.

#### **A. Pharmacoepidemiologic Studies**

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-crossover, or other models.<sup>21</sup> The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests prespecified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse

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<sup>21</sup> *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004 ([http://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](http://www.pharmacoepi.org/resources/guidelines_08027.cfm))

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event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the premarketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated prior to marketing (e.g., to study the natural history of disease or patterns of product use, or to estimate background rates for adverse events).

For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power. Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000 (an exception may be larger trials conducted for some vaccines, which could move the threshold to 1:10,000). It may also be difficult to use clinical trials: (1) to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications, or (2) to identify certain risk factors for a particular adverse event. On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials may be preferable to observational studies.

Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high.

Because different products pose different benefit-risk considerations (e.g., seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be made on a case-by-case basis. When an important adverse event–product association leads to questions on the product’s benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest.

When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding. Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study.<sup>22</sup> Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different designs. Agreement of the results from more than one study helps to provide reassurance that the observed results are robust.

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<sup>22</sup> See, for example, Strom BL (ed), 2000, *Pharmacoepidemiology*, 3<sup>rd</sup> edition, Chichester: John Wiley and Sons, Ltd; Hartzema AG, Porta M, and Tilson HH (eds), 1998, *Pharmacoepidemiology: An Introduction*, 3<sup>rd</sup> edition, Cincinnati, OH: Harvey Whitney Books.

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There are a number of references describing methodologies for pharmacoepidemiologic studies, discussing their strengths and limitations,<sup>23</sup> and providing guidelines to facilitate the conduct, interpretation, and documentation of such studies.<sup>24</sup> Consequently, this guidance document does not comprehensively address these topics. However, a protocol for a pharmacoepidemiologic study generally includes:

1. Clearly specified study objectives;
2. A critical review of the literature; and
3. A detailed description of the research methods, including:
  - the population to be studied;
  - the case definitions to be used;
  - the data sources to be used (including a rationale for data sources if from outside the U.S.);
  - the projected study size and statistical power calculations; and
  - the methods for data collection, management, and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such as data from previously conducted clinical trials or large databases. In recent years, a number of pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO, Medicaid) that allow retrieval of records on product exposure and patient outcomes. In addition, recently, comprehensive electronic medical record databases have also been used for studying drug safety issues. Depending on study objectives, factors that may affect the choice of databases include the following:

1. Demographic characteristics of patients enrolled in the health plans (e.g., age, geographic location);
2. Turnover rate of patients in the health plans;
3. Plan coverage of the medications of interest;
4. Size and characteristics of the exposed population available for study;
5. Availability of the outcomes of interest;
6. Ability to identify conditions of interest using standard medical coding systems (e.g., International Classification of Diseases (ICD-9)), procedure codes or prescriptions that could be used as markers;

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<sup>23</sup> Ibid.

<sup>24</sup> *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004 ([http://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](http://www.pharmacoepi.org/resources/guidelines_08027.cfm)).

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7. Access to medical records; and
8. Access to patients for data not captured electronically.

For most pharmacoepidemiologic studies, FDA recommends that sponsors validate diagnostic findings through a detailed review of at least a sample of medical records. If the validation of the specific outcome or exposure of interest using the proposed database has been previously reported, FDA recommends that the literature supporting the validity of the proposed study be submitted for review.

FDA encourages sponsors to communicate with the Agency when pharmacoepidemiologic studies are being developed.

### **B. Registries**

The term *registry* as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects.”<sup>25</sup> Whenever possible, a control or comparison group should be included, (i.e., individuals with a disease or risk factor who are not treated or are exposed to medical interventions other than the intervention of interest).<sup>26</sup>

Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics.<sup>27</sup>

Registries can be particularly useful for:

1. Collecting outcome information not available in large automated databases; and
2. Collecting information from multiple sources (e.g., physician records, hospital summaries, pathology reports, vital statistics), particularly when patients receive care from multiple providers over time.

A sponsor can initiate a registry at any time. It may be appropriate to initiate the registry at or before initial marketing, when a new indication is approved, or when there is a need to evaluate

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<sup>25</sup> See Frequently Asked Questions About Medical and Public Health Registries, The National Committee on Vital and Health Statistics, at <http://www.ncvhs.hhs.gov>.

<sup>26</sup> See for example, FDA Guidance for Industry, *Establishing Pregnancy Exposure Registries*, August 2002 <http://www.fda.gov/cder/guidance/3626fnl.pdf>.

<sup>27</sup> Ibid.

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safety signals identified from spontaneous case reports. In deciding whether to establish a registry, FDA recommends that a sponsor consider the following factors:

1. The types of additional risk information desired;
2. The attainability of that information through other methods; and
3. The feasibility of establishing the registry.

Sponsors electing to initiate a registry should develop written protocols that provide: (1) objectives for the registry, (2) a review of the literature, and (3) a summary of relevant animal and human data. FDA suggests that protocols also contain detailed descriptions of: (1) plans for systematic patient recruitment and follow-up, (2) methods for data collection, management, and analysis, and (3) conditions under which the registry will be terminated. A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity, and validation of registry findings against a sample of medical records or through interviews with health care providers. FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study and we encourage sponsors to discuss their registry development plans with FDA.

### **C. Surveys**

Patient or health care provider surveys can gather information to assess, for example:

1. A safety signal;
2. Knowledge about labeled adverse events;
3. Use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist;
4. Compliance with the elements of a RiskMAP (e.g., whether or not a Medication Guide was provided at the time of product dispensing); and<sup>28</sup>
5. Confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names.

Like a registry, a survey can be initiated by a sponsor at any time. It can be conducted at the time of initial marketing (i.e., to fulfill a postmarketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

FDA suggests that sponsors electing to initiate a survey develop a written protocol that provides objectives for the survey and a detailed description of the research methods, including: (1) patient or provider recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management, and analysis.<sup>29</sup> FDA recommends that a survey-based monitoring

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<sup>28</sup> For a detailed discussion of RiskMAP evaluation, please consult the *RiskMAP Guidance*.

<sup>29</sup> See 21 CFR parts 50 and 56 for FDA's regulations governing the protection of human subjects.

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system include carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers, whenever possible. FDA recommends that survey instruments be validated or piloted before implementation. FDA suggests that sponsors consider whether survey translation and cultural validation would be important.

Sponsors are encouraged to discuss their survey development plans with FDA.

### **VI. INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK**

After identifying a safety signal, FDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also: (1) employ data mining techniques, and (2) calculate reporting rates for comparison to background rates. Based on these findings and other available data (e.g., from preclinical or other sources), FDA suggests that a sponsor consider further study (e.g., observational studies) to establish whether or not a potential safety risk exists.

When evaluation of a safety signal suggests that it may represent a potential safety risk, FDA recommends that a sponsor submit a synthesis of all available safety information and analyses performed, ranging from preclinical findings to current observations. This submission should include the following:

1. Spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;
2. Background rate for the event in general and specific patient populations, if available;
3. Relative risks, odds ratios, or other measures of association derived from pharmacoepidemiologic studies;
4. Biologic effects observed in preclinical studies and pharmacokinetic or pharmacodynamic effects;
5. Safety findings from controlled clinical trials; and
6. General marketing experience with similar products in the class.

After the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event. FDA suggests that the sponsor's submission provide an assessment of the benefit-risk balance of the product for the population of users as a whole and for identified at-risk patient populations, and, if appropriate, (1) propose steps to further investigate the signal through additional studies, and (2) propose risk

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minimization actions.<sup>30</sup> FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class) and will communicate its conclusions to the sponsor whenever possible. Factors that are typically considered include:

1. Strength of the association (e.g., relative risk of the adverse event associated with the product);
2. Temporal relationship of product use and the event;
3. Consistency of findings across available data sources;
4. Evidence of a dose-response for the effect;
5. Biologic plausibility;
6. Seriousness of the event relative to the disease being treated;
7. Potential to mitigate the risk in the population;
8. Feasibility of further study using observational or controlled clinical study designs; and
9. Degree of benefit the product provides, including availability of other therapies.

As noted in section II, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps.<sup>31</sup> FDA recommends that assessment of causality and of strategies to minimize product risk occur on an ongoing basis, taking into account the findings from newly completed studies.

## **VII. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN**

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket requirements under the FDCA and FDA implementing regulations) is sufficient for postmarketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A

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<sup>30</sup> In the vast majority of cases, risk communication that incorporates appropriate language into the product's labeling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a RiskMAP. Please refer to the *RiskMAP Guidance* for a complete discussion of RiskMAP development.

<sup>31</sup> For additional discussion of the relationship between risk assessment and risk minimization, please consult the *RiskMAP Guidance*.

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pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.<sup>32</sup> The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. The likelihood that the adverse event represents a potential safety risk;
2. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);
3. The severity of the event;
4. The nature of the population(s) at risk;
5. The range of patients for which the product is indicated (broad range or selected populations only); and
6. The method by which the product is dispensed (through pharmacies or performance linked systems only).<sup>33</sup>

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (RiskMAP), as described in the *RiskMAP Guidance*. Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product's pharmacovigilance plan.

FDA believes that for a product without safety risks identified pre- or post-approval and for which at-risk populations are thought to have been adequately studied, routine spontaneous reporting will be sufficient for postmarketing surveillance. On the other hand, pharmacovigilance plans may be appropriate for products for which: (1) serious safety risks have been identified pre- or post-approval, or (2) at-risk populations have not been adequately studied.

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<sup>32</sup> As used in this document, the term "pharmacovigilance plan" is defined differently than in the ICH draft E2E document (version 4.1). As used in the ICH document, a "pharmacovigilance plan" would be routinely developed (i.e., even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks. This ICH guidance is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November, 2004.

<sup>33</sup> For a detailed discussion of controlled access systems, please consult the *RiskMAP Guidance*.

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Sponsors may discuss with the Agency the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

1. Submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e., as 15-day reports);
2. Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually);
3. Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be (1) drug based: identifying adverse events in patients taking certain products, (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or (3) event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure);
4. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs (see section V);
5. Creation of registries or implementation of patient or health care provider surveys (see section V); and
6. Additional controlled clinical trials.<sup>34</sup>

As data emerges, FDA recommends that a sponsor re-evaluate the safety risk and the effectiveness of its pharmacovigilance plan. Such re-evaluation may result in revisions to the pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions on potential safety risks and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee or the FDA Advisory Committee dealing with the specific product in question. Such committees may be convened when FDA seeks: (1) general advice on the design of pharmacoepidemiologic studies, (2) comment on specific pharmacoepidemiology studies developed by sponsors or FDA for a specific product and safety question, or (3) advice on the interpretation of early signals from a case series and on the need for further investigation in pharmacoepidemiologic studies. While additional information is being developed, sponsors working with FDA can take interim actions to communicate information about potential safety risks (e.g., through labeling) to minimize the risk to users of the product.

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<sup>34</sup> For a discussion of risk assessment in controlled clinical trials, please consult the *Premarketing Guidance*.

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# **Guidance for Industry**

## **E2E Pharmacovigilance Planning**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**April 2005  
ICH**

# Guidance for Industry

## E2E Pharmacovigilance Planning

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**April 2005  
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## **Guidance for Industry<sup>1</sup>**

### **E2E Pharmacovigilance Planning**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### **I. INTRODUCTION (1, 1.1)<sup>2</sup>**

This guidance is intended to aid in planning pharmacovigilance activities, especially in preparation for the early postmarketing period of a new drug (in this guidance, the term *drug* denotes chemical entities, biotechnology-derived products, and vaccines). The main focus of this guidance is on a safety specification and pharmacovigilance plan that might be submitted at the time of license application. The guidance can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the safety specification and pharmacovigilance plan into the Common Technical Document (CTD).

The guidance describes a method for summarizing the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied preapproval. It proposes a structure for a pharmacovigilance plan and sets out principles of good practice for the design and conduct of observational studies. It does not describe other methods to reduce risks from drugs, such as risk communication. The guidance takes into consideration ongoing work in the three regions and beyond on these issues.

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<sup>1</sup> This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2004. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

<sup>2</sup> Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2004.

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This guidance does not cover the entire scope of pharmacovigilance. It uses the World Health Organization (WHO) definition of the term *pharmacovigilance* as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.” This definition encompasses the use of pharmacoepidemiological studies.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

### **A. Background (1.2)**

The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed. In particular, during the early postmarketing period, the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a product is marketed, new information will be generated, which can have an impact on the benefits or risks of the product; evaluation of this information should be a continuing process, in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of medicines in a timely manner.

Industry and regulators have identified the need for better and earlier planning of pharmacovigilance activities before a product is approved or a license is granted. This ICH guidance has been developed to encourage harmonization and consistency and prevent duplication of effort and could be of benefit to public health programs throughout the world as they consider new drugs in their countries.

### **B. Scope of the Guidance (1.3)**

The guidance could be most useful for new chemical entities, biotechnology-derived products, and vaccines, as well as for significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnology-derived product) and for established products that are to be introduced to new populations or in significant new indications or where a new major safety concern has arisen.

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The purpose of this guidance is to propose a structure for a pharmacovigilance plan and a safety specification that summarizes the identified and potential risks of the product to be addressed in the plan. The guidance is divided into the following sections:

- Safety specification
- Pharmacovigilance plan
- Annex — Pharmacovigilance Methods

It is recommended that company pharmacovigilance experts get involved early in product development. Planning and dialogue with regulators should also start long before license application. A safety specification and pharmacovigilance plan can also be developed for products already on the market (e.g., new indication or major new safety concern). The plan could be used as the basis for discussion of pharmacovigilance activities with regulators in the different ICH regions and beyond.

For products with important identified risks, important potential risks or important missing information, the pharmacovigilance plan should include additional actions designed to address these concerns. For products for which no special concerns have arisen, routine pharmacovigilance as described in section III.A.2 (3.1.2) of this guidance should be sufficient for postapproval safety monitoring, without the need for additional actions (e.g., safety studies).

During the course of implementing the various components of the plan, any important emerging benefit or risk information should be discussed and used to revise the plan.

The following principles underpin this guidance:

- Planning of pharmacovigilance activities throughout the product life-cycle
- Science-based approach to risk documentation
- Effective collaboration between regulators and industry
- Applicability of the pharmacovigilance plan across the three ICH regions

## **II. SAFETY SPECIFICATION (2)**

The safety specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions that warrant further investigation to refine understanding of the benefit-risk profile during the postapproval period. This safety specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the pharmacovigilance plan. The safety specification can be built initially during the premarketing phase and, at the time approval is sought, it should reflect the status of issues that were being followed during development.

The Common Technical Document (CTD), especially the Overview of Safety (2.5.5), Benefits and Risks Conclusions (2.5.6), and the Summary of Clinical Safety (2.7.4) sections, includes information relating to the safety of the product and should be the basis of the safety issues identified in the safety specification. Sponsors should support the safety specification with

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references to specific pages of the CTD or other relevant documents. The safety specification can be a stand-alone document, usually in conjunction with the pharmacovigilance plan, but elements can also be incorporated into the CTD. The length of the document will generally depend on the product and its development program. Appendices can be added if it is considered important to provide a more detailed explanation of important risks or analyses.

### **A. Elements of the Safety Specification (2.1)**

It is recommended that sponsors follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development program. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

The focus of the safety specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered for inclusion.

#### *1. Nonclinical (2.1.1)*

Within the Specification, this section should present nonclinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity, etc.)
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.)
- Drug interactions
- Other toxicity-related information or data

If the product is intended for use in special populations, consideration should be given to whether specific nonclinical data needs exist.

#### *2. Clinical (2.1.2)*

##### *a. Limitations of the human safety database*

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

The worldwide experience should be briefly discussed, including:

- The extent of the worldwide exposure
- Any new or different safety issues identified
- Any regulatory actions related to safety

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### b. Populations not studied in the preapproval phase

The specification should discuss which populations have not been studied or have only been studied to a limited degree in the preapproval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed (CTD 2.5.5). Populations to be considered should include (but might not be limited to):

- Children
- The elderly
- Pregnant or lactating women
- Patients with relevant co-morbidity such as hepatic or renal disorders
- Patients with disease severity different from that studied in clinical trials
- Sub-populations carrying known and relevant genetic polymorphism
- Patients of different racial and/or ethnic origins

### c. Adverse events (AEs)/adverse drug reactions (ADRs)

This section should list the important identified and potential risks that require further characterization or evaluation. Specific references should be made to guide a reviewer to where clinical safety data are presented (e.g., relevant sections of the CTD 2.5.5 and 2.7.4).

Discussion of risk factors and potential mechanisms that apply to identified AEs/ADRs should draw on information from any part of the CTD (nonclinical and clinical) and other relevant information, such as other drug labels, scientific literature, and postmarketing experience.

#### ***Identified risks for further evaluation***

More detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These AEs/ADRs should usually call for further evaluation as part of the pharmacovigilance plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups).

#### ***Potential risks for further evaluation***

Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterize the association.

### d. Identified and potential interactions, including food-drug and drug-drug interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarized, and the potential health risks posed for the different indications and in the different populations should be discussed.

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### e. Epidemiology

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed (because the epidemiology of the indication(s) may vary across regions), if this information is available.

In addition, for important adverse events that may require further investigation, it is useful to review the incidence rates of these events among patients in whom the drug is indicated (i.e., the background incidence rates). For example, if condition X is an important adverse event in patients who are treated with drug Y for disease Z, then it is useful to review the incidence of condition X in patients with disease Z who are not treated with drug Y; this is the background rate of condition X among patients with disease Z. Information on risk factors for an adverse event (condition X) would also be useful to include, if available.

### f. Pharmacological class effects

The safety specification should identify risks believed to be common to the pharmacological class.

## **B. Summary (2.2)**

At the end of the safety specification, a summary should be provided of the:

- Important identified risks
- Important potential risks
- Important missing information

Sponsors are encouraged to summarize specific ongoing safety issues on an issue-by-issue basis, including both nonclinical and clinical data that are pertinent to the problem.

## **III. PHARMACOVIGILANCE PLAN (3)**

This section gives guidance on the structure of a pharmacovigilance plan. The pharmacovigilance plan should be based on the safety specification. The specification and plan can be written as two parts of the same document. The plan would normally be developed by the sponsor and can be discussed with regulators during product development, prior to approval (i.e., when the marketing application is submitted) of a new product, or when a safety concern arises postmarketing. It can be a stand-alone document, but elements could also be incorporated into the CTD.

For products for which no special concerns have arisen, routine pharmacovigilance as described in section III.A.2 (3.1.2) of this guidance should be sufficient for postapproval safety monitoring, without the need for additional actions (e.g., safety studies). However, for products with

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important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered.

The length of the document will likely depend on the product and its development program. The pharmacovigilance plan should be updated as important information on safety becomes available and milestones are reached.

### **A. Structure of the Pharmacovigilance Plan (3.1)**

Outlined below is a suggested structure for the pharmacovigilance plan. The structure can be varied depending on the product in question and the issues identified in the safety specification.

#### *1. Summary of Ongoing Safety Issues (3.1.1)*

At the beginning of the pharmacovigilance plan, a summary should be provided of the:

- Important identified risks
- Important potential risks
- Important missing information

This is important if the pharmacovigilance plan is a separate document from the safety specification.

#### *2. Routine Pharmacovigilance Practices (3.1.2)*

Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a pharmacovigilance plan. This routine pharmacovigilance should include the following:

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner
- The preparation of reports for regulatory authorities:
  - Expedited adverse drug reaction (ADR) reports
  - Periodic safety update reports (PSURs)
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities
- Other requirements, as defined by local regulations

In some ICH regions, there might be a regulatory requirement to present within the pharmacovigilance plan an overview of the company's organization and practices for conducting pharmacovigilance. In the absence of such a requirement, a statement that the company's routine

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pharmacovigilance practices include the elements outlined in the bulleted list above should be sufficient.

#### *3. Action Plan for Safety Issues (3.1.3)*

The plan for each important safety issue should be presented and justified according to the following structure:

- Safety issue
- Objective of proposed action(s)
- Action(s) proposed
- Rationale for proposed action(s)
- Monitoring by the sponsor for safety issue and proposed action(s)
- Milestones for evaluation and reporting

Any protocols for specific studies can be provided in the CTD section 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., Module 4 if the study is a nonclinical study).

#### *4. Summary of Actions To Be Completed, Including Milestones (3.1.4)*

An overall pharmacovigilance plan for the product bringing together the actions for all individual safety issues should be presented. Whereas section 3.1.3 suggests presenting an action plan by ongoing safety issue, for this section the pharmacovigilance plan for the product should be organized in terms of the actions to be undertaken and their milestones. The reason for this is that one proposed action (e.g., a prospective safety cohort study) could address more than one of the identified issues.

It is recommended that milestones for completion of studies and other evaluations, and for submission of safety results, be included in the pharmacovigilance plan. In developing these milestones, one should consider when:

- Exposure to the product will have reached a level sufficient to allow potential identification/characterization of the AEs/ADRs of concern or resolution of a particular concern, and/or
- The results of ongoing or proposed safety studies are expected to be available.

These milestones might be aligned with regulatory milestones (e.g., PSURs, annual reassessment and license renewals) and used to revise the pharmacovigilance plan.

### **B. Pharmacovigilance Methods (3.2)**

The best method to address a specific situation can vary, depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk, or missing information is the issue and whether signal detection, evaluation, or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, sponsors should employ the most

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appropriate design. The Annex provides a summary of the key methods used in pharmacovigilance. This is provided to aid sponsors considering possible methods to address specific issues identified by the safety specification. This list is not all-inclusive, and sponsors should use the most up-to-date methods that are relevant and applicable.

#### *Design and Conduct of Observational Studies (3.2.1)*

Carefully designed and conducted pharmacoepidemiological studies, specifically observational (noninterventional, nonexperimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator “observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice.”<sup>1</sup>

Before the observational study that is part of a pharmacovigilance plan commences, a protocol should be finalized. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the pharmacovigilance plan.

Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator’s interpretation of the findings.

It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology.<sup>2</sup> In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed.

The highest possible standards of professional conduct and confidentiality should always be maintained, and any relevant national legislation on data protection followed.

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**IV. REFERENCES (4)**

1. CIOMS, Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. Geneva; World Health Organization (WHO), 2001.
2. Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, [http://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](http://www.pharmacoepi.org/resources/guidelines_08027.cfm), August 2004.

## **ANNEX — PHARMACOVIGILANCE METHODS**

### **1. Passive Surveillance**

- **Spontaneous Reports**

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g., WHO, regional centers, poison control center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.<sup>1</sup>

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other premarketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.<sup>2,3,4,5</sup>

#### *Systematic Methods for the Evaluation of Spontaneous Reports*

More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection.<sup>6,7,8</sup> Data mining techniques have also been used to examine drug-drug interactions.<sup>9</sup> Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

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- **Case Series**

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome.<sup>10, 11</sup> Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

### **2. Stimulated Reporting**

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods.<sup>12</sup> Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a predesigned method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early postmarketing phase, companies might actively provide health professionals with safety information, and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early postmarketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan). This should be regarded as a form of spontaneous event reporting; thus, data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

### **3. Active Surveillance**

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous preorganized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact.<sup>13</sup> In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

- **Sentinel Sites**

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting

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system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites<sup>14</sup>. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysis centers, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

- **Drug Event Monitoring**

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at prespecified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.<sup>12, 15, 16, 17</sup> Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

- **Registries**

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

Exposure (drug) registries address populations exposed to drugs of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

#### **4. Comparative Observational Studies**

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).<sup>12, 15</sup>

- **Cross-sectional Study (Survey)**

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

- **Case-control Study**

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction, that might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

- **Cohort Study**

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but nonexposed at another time point. Since the population exposure during follow-up

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is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes. Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

There are several automated databases available for pharmacoepidemiologic studies.<sup>12, 15, 18</sup> They include databases that contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets might include millions of patients. Since they are created for administrative or billing purposes, they might not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

### **5. Targeted Clinical Investigations**

When significant risks are identified from preapproval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from preapproval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the event of interest will be

## *Contains Nonbinding Recommendations*

focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. Large, simplified trials are also resource-intensive.

### **6. Descriptive Studies**

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

- **Natural History of Disease**

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective.<sup>15</sup> For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

- **Drug Utilization Study**

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes.<sup>12</sup> These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

## *Contains Nonbinding Recommendations*

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2. Pinkston V, Swain EJ, Management of adverse drug reactions and adverse event data through collection, storage, and retrieval. In Stephens MDB, Talbot JCC, and Routledge PA, eds. *Detection of New Adverse Drug Reactions*. 4<sup>th</sup> ed. 1998; MacMillan Reference Ltd, London. p 282.
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*Contains Nonbinding Recommendations*

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/s/  
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MEREDITH LIBEG  
02/04/2015



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

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Memorandum

**Date:** January 29, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Statistical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Statistical Reviewer has the following request for information. Please provide your response to me via email Wednesday, February 4, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Provide the stand-alone SAS programs that can be used to reproduce the major efficacy and safety results in the Clinical Study Reports of studies GO28141 and NO25395 and the proposed labeling.
2. Please provide a document (.pdf) that provides descriptions of analyses, the names of variables, and datasets used in those SAS programs

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
01/29/2015



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

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Memorandum

**Date:** January 28, 2015  
**From:** Meredith Libeg, Senior Regulatory Health Project Manager -  
CDER/OHOP/DOP2  
**Subject:** **NDA 206192** – Genentech, Inc.  
***Clinical Review Comments and Information Request***

---

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [*Proposed*] (Cobimetinib).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email Wednesday, January 28, 2015, if possible, and follow that with a formal submission to the NDA.

**Comments:**

1. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? If so, where in the application can this information be found?
2. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? If so, where in the application can this information be found?

If you have any questions, please feel free to contact me at [meredith.libeg@fda.hhs.gov](mailto:meredith.libeg@fda.hhs.gov) or (301.796.1721).

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/s/  
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MEREDITH LIBEG  
01/28/2015



NDA 206192

**NDA ACKNOWLEDGMENT**

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

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: Cobimetinib, tablet for oral use

Date of Application: December 11, 2014

Date of Receipt: December 11, 2014

Our Reference Number: NDA 206192

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 February 9, 2015, 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 Oncology Products 2  
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>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Chief, Project Management Staff (acting)  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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MELANIE B PIERCE  
01/05/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 206192

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cobimetinib, tablet for oral use.

We also refer to your December 17, 2014, electronic mail correspondence requesting an application orientation meeting. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a non-PDUFA meeting.

The meeting is scheduled as follows:

**Date:** Monday, January 12, 2015  
**Time:** 11:00 AM to 12:00 PM EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 2205  
Silver Spring, Maryland 20903

**FDA Participants** are as follows:

Richard Pazdur	Olen Stephens
Patricia Keegan	Sue Kang
Joseph Gootenberg	Monica Hughes
Marc Theoret,	Frances Fahnbulleh
Ruthann Giusti	Lauren Iacono-Connors
Whitney Helms	Rajeshwari Sridhara
Anwar Goheer	Elizabeth Mansfield
Hong Zhao	Reena Philip
Ruby Leong	Robert Becker
Kun He	Donna Roscoe
Janet Jiang	Somesh Chattopadhyay
Ali Al Hakim	
Donghao Lu	
Liang Zhou	

Jeffery Summers

If you have any questions, call me at (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Chief, Project Management Staff (acting)  
Division of Oncology Products 2  
Office of Hematology and Oncology Drug Products  
Center for Drug Evaluation and Research

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MELANIE B PIERCE  
12/19/2014



NDA 206192

**ACKNOWLEDGE NDA PRESUBMISSION**

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Cobimetinib in combination with vemurafenib

Date of Submission: October 30, 2014

Date of Receipt: October 30, 2014

Our Reference Number: NDA 206192

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA listed above at the top of the first page of any communications concerning this application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to

set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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MELANIE B PIERCE  
11/19/2014



IND 109307

**MEETING MINUTES**

Hoffman La-Roche, Inc.  
Attention: Sarah Wayson, PhD  
Regulatory Program Management  
Genentech, Inc.  
1 DNA Way, MS 241B  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zelboraf (vemurafenib) and cobimetinib.

We also refer to the meeting between representatives of your firm and the FDA on October 8, 2014. The purpose of the meeting was to obtain the Agency's guidance on the acceptability of the clinical trial results from study GO28141 and supporting studies to form the basis of an NDA for cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600-mutation.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products 2  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** October 8, 2014; 1:00 PM  
**Meeting Location:** CDER WO Bldg 22; room 1313

**Application Number:** IND 109307  
**Product Name:** Cobimetinib (GDC-0973)  
**Indication:** Treatment of patients with unresectable or metastatic melanoma with BRAFV600-mutation.

**Sponsor/Applicant Name:** Hoffman-La Roche

**Meeting Chair:** Marc Theoret, M.D.  
**Meeting Recorder:** Melanie Pierce

**FDA ATTENDEES**

**Office of Hematology Oncology Products**

**Division of Oncology Products 2**

Patricia Keegan, MD	Director
Marc Theoret, MD	Team Leader
Ruthann Giusti, MD	Clinical Reviewer
Deveonne Hamilton-Stokes, RN, BSN	Project Manager
Rebecca Cohen, RN, MPH	Project Manager
Leah Her, MS	Project Manager
Monica Hughes, MS	Chief, Project Management Staff
Melanie Pierce, BSc	Project Manager

**Office of Hematology Oncology Products**

**Division of Hematology Oncology Toxicology**

Whitney Helms, PhD	Pharmacology/Toxicology Supervisor
Anwar Goheer, PhD	Pharmacology/Toxicology Reviewer

**Office of Clinical Pharmacology V**

Hong Zhao, PhD	Clinical Pharmacology Team Leader
Ruby Leong, PhD	Clinical Pharmacology Reviewer

**Office of Biostatistics**

**Division of Biostatistics V**

Kun He, PhD

Statistical Team Leader

Janet Jiang, PhD

Statistical Reviewer

**Office of New Drugs Quality Assessment**

Ali Al Hakim, PhD

Branch Chief

**Office of Surveillance and Epidemiology:**

Amarilys Vega, MD

Medical Officer

Frances Fahnbulleh

Project Manager

**Office of Scientific Investigations**

Lauren Iacono-Connors, PhD

Microbiologist

**Center for Devices & Radiological Health (CDRH)**

Donna Roscoe, PhD

Branch Chief

Caryl Giuliano, PhD

CDRH Reviewer

**GENENTECH ATTENDEES**

Ilsung Chang, Ph.D.

Biostatistics, Lead

Edna Choo, Ph.D.

Drug Metabolism and Pharmacokinetics, Lead

Susan Eng, Pharm.D.

Safety Science, Lead

Steve Hack, M.D., Ph.D.

Clinical Science, Study Lead

Eric Harstad, Ph.D., DABT

Nonclinical, Safety Assessment Lead

Carmen Ladner

Regulatory Affairs, Senior Director

Theodora Lambros, M.S.

Regulatory Affairs, Associate

Kavita Mistry, Ph.D.

Technical Regulatory, Lead

Luna Musib, Ph.D.

Clinical Pharmacology, Lead

Mika Sovak, M.D., Ph.D.

Clinical Science, Global Development Lead

Sarah Wayson, Ph.D.

Regulatory Affairs, U.S. Lead

Xian Zhou, Ph.D.

Biostatistics, Associate Director

## BACKGROUND

### Regulatory Background:

The following represent key regulatory landmark interactions with Hoffman-La Roche:

On June 12, 2012, an End-of-Phase 1/Pre-Phase 3 meeting was held with the FDA to discuss the proposed development plan for cobimetinib (GDC-0973), for use in combination with vemurafenib, for the treatment of patients with unresectable or metastatic melanoma with activating BRAF-mutations and to obtain FDA's feedback on the appropriate regulatory strategy.

On November 27, 2012, end-of-Phase 2 meeting to discuss the cobimetinib CMC data and to obtain FDA's feedback on proposals for the product manufacture and development of cobimetinib in preparation for the planned initial NDA submission for BRAF V600-mutation-positive, unresectable or metastatic melanoma.

On April 22, 2013, FDA issued Written Responses to a Type C meeting request to confirm the suitability of the proposed clinical pharmacology studies to support the use of in combination with vemurafenib.

On November 29, 2013, FDA issued Written Responses in response to a Type C meeting request to discuss general content and format issues for a proposed NDA to support the approval of vemurafenib in combination with cobimetinib for the treatment of patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma.

On March 5, 2014, a CMC pre-NDA meeting was held to obtain the Agency's feedback on proposals for the development with regard to product characterization and manufacture of cobimetinib in preparation for the planned NDA for advanced BRAF V600 mutation-positive, unresectable or metastatic melanoma.

On March 14, 2014, Hoffman-La Roche submitted a [REDACTED] (b) (4) request for cobimetinib, in combination with Zelboraf (vemurafenib), for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. [REDACTED] (b) (4)

On June 17, 2014, Hoffman-La Roche submitted a request for Fast Track Designation (FTD) for cobimetinib for use with vemurafenib for the treatment of patients with BRAF V600 mutated unresectable or metastatic melanoma. Cobimetinib received designation for the Fast Track Development program for the investigation of cobimetinib and vemurafenib for the treatment of patients with BRAF V600E-mutation positive, unresectable or metastatic melanoma to demonstrate improved progression-free survival and overall survival on August 15, 2014.

On July 23, 2014, Hoffman-La Roche requested a meeting to obtain the Agency's guidance on the acceptability of the clinical trial results from study GO28141 and supporting studies to form the basis of a NDA submission for the use of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic BRAFV600 mutated melanoma.

**Chemical Description:**

Cobimetinib (GDC-0973) is a small molecule inhibitor of the mitogen-activated protein kinase (MEK1/2). For the purposes of the NDA submission, cobimetinib drug product will be supplied as a 20-mg film-coated immediate-release tablet for oral administration. Cobimetinib has also been evaluated in clinical trials as a capsule presentation, in a hard gelatin capsule shell.

Clinical studies supporting the proposed NDA for cobimetinib in combination with vemurafenib  
The clinical studies which support the proposed NDA for cobimetinib are listed in Table 17 below which is abstracted from section 14.2 on page 90 of the meeting package provided by Hoffmann-LaRoche:

**Table 17 Clinical Studies Supporting the Proposed New Drug Application for Cobimetinib in Advanced BRAF Mutated Melanoma**

Clinical Study	n	Patient Population	Regimen	CSR or Individual Study Safety Summaries	Clinical Cutoff Date Month/Day/Year	SCE	SCS	CRFs	Datasets
GO28141 (Phase III)	495	BRAFV600-Mutated Melanoma,	Cobimetinib 60 21/7 + vemurafenib 960 or placebo BID	CSR	5/9/14	Yes	Yes	Yes	Raw and derived datasets
NO25395 (Phase Ib)	131 <sup>a</sup>	BRAFV600-mutated melanoma	Cobimetinib 60 21/7 and other dosing regimens + vemurafenib 960 or 720 mg BID	CSR	10/1/13	Yes	Yes	Yes	Raw and derived datasets
MEK4592g (Phase I)	115	Locally advanced or metastatic solid tumors	Various doses of cobimetinib on 21/7 and 14/14 schedule, including 20 patients in a DDI cohort	2 CSRs <sup>b</sup>	5/25/12 & 6/11/13	No	Yes	Yes	Raw and derived datasets
MEK4952g (Phase I)	12	Healthy volunteers	Absolute bioavailability study <sup>d</sup>	CSR	4/20/11	No	No	No <sup>c</sup>	Yes
MEK4953g (Phase I)	20	Healthy volunteers	Relative bioavailability and food effect <sup>d</sup>	CSR	4/20/11	No	No	No <sup>c</sup>	Yes

Clinical Study	n	Patient Population	Regimen	CSR or Individual Study Safety Summaries	Clinical Cutoff Date Month/Day/Year	SCE	SCS	CRFs	Datasets
GP28369 (Phase I)	6	Healthy volunteers	Mass balance <sup>d</sup>	CSR	2/8/13	No	No	No <sup>c</sup>	Yes
MEK4954g (Phase I)	20	Healthy volunteers	Effect of proton pump inhibitors on cobimetinib <sup>d</sup>	CSR	7/7/11	No	No	No <sup>c</sup>	Yes
GP28620 (Phase I)	16	Healthy volunteers	Effect of itraconazole on cobimetinib <sup>d</sup>	CSR	10/4/13	No	No	No <sup>c</sup>	Yes
GP28370 (Phase I)	28	Healthy volunteers	Relative Bioavailability Study <sup>d</sup>	CSR	TBD	No	No	No <sup>c</sup>	Yes

The GO28141 (coBRIM) trial is intended to provide the primary safety and efficacy data in support of the proposed NDA. Trial NO25395 (BRIM7) will provide supportive activity and safety data for the combination of cobimetinib and vemurafenib. Trial MEK4592g will provide safety data on cobimetinib. Selected safety data will also be submitted from two ongoing trials

(b) (4)

Trial GO28141 (COBRIM):

This trial is a randomized (1:1), multicenter, double-blind, placebo-controlled trial that enrolled treatment-naïve patients with unresectable locally advanced or metastatic melanoma, containing a BRAF V600E mutation detected using an FDA-approved real-time polymerase chain reaction assay (cobas® 4800 BRAFV600 Mutation Test, Hoffman-La Roche Molecular Systems, Branchburg, NJ, USA). In this trial, Patients were randomly assigned in a 1:1 ratio to two treatment arms:

- Experimental arm: vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib (GDC-0973) 60 mg PO QD on Days 1–21 of each 28-day treatment cycle.
- Control arm: vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1–28 and placebo PO once daily (QD) on Days 1–21 of each 28-day treatment cycle.

Treatment continued until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurred earliest. Patients on the control arm were not allowed to receive cobimetinib at the time of investigator-assessed disease progression. Randomization was stratified by geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c) (yes vs. no).

Patients on the vemurafenib/placebo treatment arm were not allowed to receive cobimetinib at the time of investigator-assessed disease progression.

The primary endpoint of progression-free survival (PFS) as assessed by clinical investigators every 8 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The sample size of assumptions were a median PFS of 5 months in the vemurafenib plus placebo arm and 11 months in the vemurafenib plus cobimetinib arm; thus the final analysis will require 206 PFS events to detect a hazard ratio of 0.55 with 95% power at a 2-sided alpha level of 5%. The primary analysis, a stratified log-rank test was performed on the ITT population.

The key secondary endpoints are overall survival and best overall response rate (BORR). Assuming a median OS of 15 months in the vemurafenib plus placebo arm and 20 months in the vemurafenib plus cobimetinib arm, at the time of the final analysis (385 deaths) the trial had 80% power to detect a hazard ratio of 0.75 with at a 2-sided alpha level of 5%. Two interim analyses of survival were planned, the first at the final PFS analysis and the second after the occurrence of 256 (67%) deaths. The O'Brien-Fleming boundary method was utilized to control type I error, with respective alpha allocations of 0.000085 and 0.012 for the first and second interim analyses and 0.0463 at the final analysis.

A hierarchical procedure was used to adjust for multiplicity testing of the secondary endpoints of BORR and OS. PFS as assessed by blinded independent review was also to be evaluated.

Efficacy Summary:

A total of 495 patients were enrolled. As presented by Hoffmann-LaRoche, the trial demonstrated a robust improvement in investigator-assessed PFS [HR 0.51 (95% CI: 0.38, 0.68); stratified log-rank  $p < 0.0001$ ] in favor of the cobimetinib/vemurafenib arm. The median PFS

was 9.9 months in the cobimetinib plus vemurafenib arm and 6.2 months in the placebo/vemurafenib arm.

PFS as assessed by independent review was consistent with the investigator-assessed results [HR 0.60 (95% CI: 0.45, 0.80); log-rank  $p = 0.0003$ ] with median PFS times of 11.3 months in the cobimetinib/vemurafenib arm of and 6.0 months for the placebo/vemurafenib arm.

Hoffmann-LaRoche states the treatment effect of cobimetinib/vemurafenib on PFS was observed across all subgroups prespecified in the statistical analysis plan (SAP).

ORR as determined by the investigator was significantly higher in patients treated with cobimetinib than in patients treated with placebo [(68% vs. 45%;  $p < 0.0001$ ); the complete response rates were 10% with the combination compared and 4% with vemurafenib alone.

There were 34 deaths patients (13.8%) in the cobimetinib/vemurafenib arm and in 51 deaths (20.6%) of patients in the placebo/ vemurafenib arm. The first interim analysis of OS did not cross the pre-specified stopping boundary and median OS has not been reached for either arm.

#### Safety Summary:

Hoffmann LaRoche claims that cobimetinib/vemurafenib was well tolerated in Study GO28141 with an increased frequency of adverse events (AEs) in the combination arm compared with vemurafenib alone.

- The frequency of Grade 3-5 AE was higher (65% vs. 59%) among cobimetinib/vemurafenib-treated patients than for vemurafenib-treated patients.
- The frequency of serious adverse events (SAEs) was higher (30% vs. 25%) for cobimetinib/vemurafenib-treated patients than vemurafenib-treated patients.
- There were six deaths during or within 30 days of study treatment among cobimetinib/vemurafenib-treated patients arm and three deaths among vemurafenib-treated patients. Two deaths patients in each arm were attributed to progressive disease.

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PREAMBLE: The Sponsor of record for this meeting, as per the form FDA 1571 for the IND is Hoffman-La Roche. However, in the October 8, 2014 correspondence submitted in response to FDA's preliminary comments, sent October 7, 2014, the sponsor identified themselves as Genentech. Therefore, in the sections of the meeting minutes referring to the October 8, 2014, correspondence, the sponsor is referred to as Genentech.

### **Sponsor Submitted Questions and FDA Response:**

#### CLINICAL and BIOSTATISTICS:

1. Does the Agency agree that the efficacy and safety results from Study GO28141 as well as supportive data from Studies NO25395, MEK4592g, and additional clinical pharmacology studies provide sufficient clinical experience to characterize the risks and benefits of cobimetinib in support of a NDA filing for the proposed indication?

**FDA Response:** The high-level efficacy and safety results as presented in the meeting briefing document appear adequate to support an NDA filing for cobimetinib. However, a determination that the data in the proposed NDA is sufficient to characterize the benefits and risks of cobimetinib when administered in combination with vemurafenib for the proposed indication requires review of the NDA.

**Discussion during the meeting:** Roche thanks FDA for the response and has no further comment.

2. Does the Agency agree with the proposal for the planned analyses and presentation of efficacy data in the Summary of Clinical Efficacy (SCE) and Integrated Summary of Efficacy (ISE) (see Section 14.4 for details)?

**FDA Response:** FDA concurs with Hoffman-La Roche's proposal to present efficacy data from Trial GO28141 and Trial NO25395 in a side-by-side table format as outlined in Section 14.4 of the meeting briefing document. However, in addition to the proposed analysis of all patients with prior vemurafenib therapy regardless of cobimetinib and vemurafenib dosage, FDA requests that the SCE and ISE provide analyses of efficacy for Study NO25395 based on the subgroup of patients who had progressed on or after vemurafenib (vem-PD) and then received the combination of vemurafenib and cobimetinib at the recommended dose and schedule (i.e., cobimetinib 60 mg orally once daily on a 21 days on/7 days off schedule plus vemurafenib 960 mg orally twice daily continuously).

**Company Response sent via email October 8, 2014:** Roche agrees to include analyses for Study NO25395 based on the subgroup of patients who had progressed on or after vemurafenib at the recommended dose and schedule.

**Discussion during the meeting:** There was no discussion during the meeting.

3. Does the Agency agree with the proposal for the planned analyses and presentation of safety data in the Summary of Clinical Safety (SCS) and Integrated Summary of Safety (ISS)?

**FDA Response:** With respect to the proposal for presentation of safety data in the Summary of Clinical Safety (SCS) and the Integrated Summary of Safety (ISS) as outlined in Section 14.5 of the meeting package, FDA has the following comments:

- a. For Study NO25395, in addition to the proposed analysis of all patients with prior vemurafenib therapy regardless of cobimetinib and vemurafenib dosage, please include a separate analysis based on the subgroup of patients who had progressed on or after vemurafenib (vem-PD) and then received the combination of vemurafenib and cobimetinib at the recommended dose and schedule (i.e., cobimetinib 60 mg orally once daily on a 21 days on/7 days off schedule plus vemurafenib 960 mg orally twice daily continuously).

- b. In the pooled safety database, please retain indicator variables to identify the study of origin, the cobimetinib and vemurafenib dose and schedule, the cumulative cobimetinib and vemurafenib doses and the percentage of the assigned dose delivered (dose intensity).

**Company Response sent via email October 8, 2014:**

- a. Genentech agrees to include analyses for Study NO25395 based on the subgroup of patients who had progressed on or after vemurafenib at the recommended dose and schedule.
- b. Genentech agrees to retain indicator variables to identify the study of origin, the cobimetinib and vemurafenib dose and schedule, the cumulative cobimetinib and vemurafenib doses and the percentage of the assigned dose delivered in the pooled safety database.

**Discussion during the meeting:** There was no discussion during the meeting.

4. In the Type C Written Feedback provided by the Agency on 29 November 2013 regarding the Sponsor's planned Content and Format of the proposed NDA, the Agency requested that the Sponsor provide all Adverse Events of Special Interest (AESIs), including secondary malignancies, identified during the review of the safety data from the supportive ongoing studies. Does the Agency agree with the Sponsor's proposed list of AESIs and Other Significant Events to be included in the SCS?

**FDA Response:** Yes, the proposed list of adverse events of special interest is acceptable as provide in Section 14.5.4. Specific advice regarding the type and forma of data to be submitted in the NDA to allow FDA to assess ocular toxicity will be provided under separate cover.

**Company Response sent via email October 8, 2014:** Genentech thanks the Agency for the confirmation of the proposed list of adverse events of special interest. Genentech would appreciate further clarification as to the Agency's comment regarding ocular toxicity and when we can expect this additional advice.

**Discussion during the meeting:** Roche inquired about the additional advice regarding ocular toxicity, FDA agreed to provide advice under separate cover. FDA stated that FDA did not have a complete listing of the information that will be requested to evaluate ocular toxicity; however, OCT scans for all patients and the study reports for those scans should be provided in the NDA for cobimetininb. FDA will clarify whether this request is limited to the pivotal study or all studies. In addition, FDA will clarify whether this should include all scans obtained or only those associated with an event post-treatment.

5. The Sponsor is considering amending the Statistical Analysis Plan (SAP) and protocol in order to conduct an earlier assessment of final OS. The Sponsor intends to submit the final OS data as a label-enabling efficacy supplement once cobimetinib receives

approval. The Sponsor would appreciate the Agency's input on the acceptability of this proposal.

**FDA Response:** In general, FDA does not agree reducing the number of events for any efficacy analyses after seeing the interim data. However, considering that the accrual is already completed, all enrolled patients will be continuously followed, and a larger treatment effect will be tested, FDA does not object to the proposed modifications.

**Company Response sent via email October 8, 2014:** Genentech thanks the Agency for the feedback and will plan to submit an amendment to the statistical analysis plan. If a statistically significant OS benefit is demonstrated at the proposed modified final analysis can the Agency comment on the ability of these data to support a label-enabling efficacy supplement?

**Discussion during the meeting:** Roche clarified that it is their intent to request inclusion of the OS data using the proposed revised statistical analysis plan (SAP). FDA stated that if the revised plan is found to be acceptable and the trial meets the specified threshold for significance as described under the revised SAP plan, OS results may be included in the label. Roche will submit the revised SAP for FDA review.

#### NONCLINICAL:

6. The Sponsor has addressed Agency feedback on the nonclinical program received at the Type B EOP1/pre-Phase III meeting held on 27 June 2012. Does the Agency agree that the nonclinical data package is now sufficiently complete to enable review and approval of the proposed indication?

**FDA Response:** The available information appears sufficient to support the filing of nonclinical section of the proposed NDA; however, a final decision regarding the acceptability of the data included in the NDA will be determined after the review of the study reports and literature.

**Discussion during the meeting:** Genentech thanked the Agency for the response and had no further comment.

#### CLINICAL PHARMACOLOGY:

7. The Sponsor has addressed Agency feedback on the clinical pharmacology program received via Type C written communications dated 22 April 2013 and 29 November 2013. Does the Agency agree that the clinical pharmacology data package is now sufficiently complete to enable review and approval of the proposed indication?

**FDA Response:** Yes, the proposed clinical pharmacology package appears acceptable to support the proposed NDA; however, the adequacy of the clinical pharmacology data will be evaluated at the time of NDA review.

**Discussion during the meeting:** Roche thanked the Agency for the response and has no further comment.

REGULATORY:

8. Given the magnitude of the treatment effect observed for cobimetinib used in combination with vemurafenib in Study GO28141, does the Agency agree that this represents a sufficient advancement in the treatment of the indicated population to qualify the proposed NDA for Priority Review?

**FDA Response:** The status of the review will be determined at the time of the filing meeting.

**Discussion during the meeting:** Roche thanked the Agency for the response and had no further comment.

9. Does the Agency agree that the proposed clinical and nonclinical content of the NDA meet the requirements for filing of a NDA according to 21 CFR 314.50?

**FDA Response:** A benefit/risk analysis must be included in the submission, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling. The remainder of the proposed submission appears to be acceptable based on the information provided in the meeting packet. However, the acceptability of the NDA for filing will be assessed at the time of the filing meeting.

**Company Response sent via email October 8, 2014:** A benefit/risk analysis in the FDA structured benefit/risk framework will be included in Section 2.5 the Clinical Overview. Additionally, a separate benefit/risk analysis will be included for the vemurafenib-progressor patients. Does the Agency agree?

**Discussion during meeting:** FDA found Roche's proposal acceptable.

10. Does the Agency agree with the proposal for submission of information prior to and during the review? Specifically:
- Fast Track Designation for cobimetinib was granted on 15 August 2014, does the Agency agree with the proposed schedule for submission.
  - Does the Agency have any recommendations that would facilitate review of the rolling submission?
  - After submission of the NDA, would the Agency like to have an orientation meeting where the Sponsor will outline the major components of the NDA?

- Assuming Priority Review is granted, the Sponsor proposes to submit the required safety update within 90 days post submission. Does the Agency agree with the content and timing of the Safety Update.

**FDA Response:** FDA does not object to the proposed schedule for submission of the NDA. FDA requests that Hoffman-La Roche formally submit the schedule for rolling submission as an amendment to the IND; FDA will respond in a separate letter.

FDA would appreciate an Application Orientation Meeting scheduled within 30 days of the NDA submission and requests that the Hoffman-La Roche be prepared to provide the review team with an overview of the datasets and variables used to produce key efficacy and safety tables and figures.

With respect to the proposed content of the Safety Update Report as described in section 14.5.7, FDA requests that the Safety Update Report include:

- a. An assessment of the impact of the additional safety data on safety profile of cobimetinib/vemurafenib.
- b. Tables presenting a side-by-side comparison of the original and updated safety data.
- c. Only one updated narrative summary per patient. Clearly identify new clinical data in the updated narratives and provide a hyperlink to the original narrative summary. Provide a listing of patients with safety updates describing new clinically significant safety information (newly reported death, study discontinuation due to toxicity, newly reported serious adverse event, etc). The listing should be linkable to the updated safety narrative and to the original safety narrative.

**Company Response sent via email October 8, 2014:** In the pre-NDA briefing package Genentech stated that Module 3, along with the corresponding Quality Summary (2.3), will be provided as part of the initial rolling submission in October. In addition, Genentech is able to provide all of Module 4 and the corresponding Nonclinical Summary documents (2.4 and 2.6), as part of the initial submission in October.

Please refer to the table below for a list of the components of the dossier that will be provided during each rolling submission:

<b>Submission Date</b>	<b>Module</b>
October 14, 2014	<b>Partial Module 1</b> Module 1.1.2 FDA Form 356h Module 1.3.2 Field Copy Certification Module 1.4.1 Letters of Authorization Module 1.12.14 Environmental Analysis

	<p><b>Partial Module 2</b> Module 2.3 (Quality Overall Summary) Module 2.4 (Nonclinical Overview) Module 2.6 (Written and Tabulated Summaries)</p> <p><b>Module 3</b> All quality documentation</p> <p><b>Module 4</b> All nonclinical pharmacology, pharmacokinetic, and toxicology reports</p>
December 11, 2014	<p><b>Remainder of Module 1</b></p> <p><b>Remainder of Module 2</b> Module 2.2 (Summary) Module 2.5 (Clinical Overview) Module 2.7 (Clinical Summary)</p> <p><b>Module 3 update</b> Module 3 P.8.1 and P.8.3 (stability)</p> <p><b>Module 5</b> All clinical documents</p>

Genentech will work with the Agency to schedule an Applicant Orientation Meeting within 30 days of the NDA submission.

Safety Update:

- (a) Genentech will provide the requested assessment.
- (b) Genentech proposes to present the original and updated safety data in in-text side-by-side tables. Does the Agency agree?
- (c) Genentech will identify new clinical data in italicized font in the updated narratives. Does the Agency agree?

**Discussion during the meeting:** Roche agreed to submit the formal request for the submission schedule of the planned rolling NDA. In addition, Roche agreed to hold an application orientation meeting within 30 days of submission of the last module submission. FDA requested that in the safety update, Roche provide new information in italicized font as addendums to the original narratives.

- 11. Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) is not required to support the use of cobimetinib for the proposed indication?

**FDA Response:** At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation

and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. The NDA can be filed without a REMS; however, please be aware that FDA will determine the need for a REMS during the review of your application.

**Discussion during the meeting:** Roche thanked the Agency for the response and had no further comment.

#### COMPANION DIAGNOSTIC:

12. Does the Agency agree that a premarket application (PMA) supplement for the FDA-approved cobas® 4800 BRAF Mutation Test is not required to support an NDA for cobimetinib?

**FDA Response:** Based on the information, and provided there are no changes to the device specific to this combination use, a PMA supplement will not be needed for the cobas® 4800 BRAF Mutation Test to support approval of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, because the test is used in accordance with its label, (i.e., to select patients eligible for vemurafenib treatment). However, if you intend to develop cobimetinib for a new indication that requires a selection of patients with BRAF V600 mutation-positive tumors, a PMA supplement will be required.

**Discussion during the meeting:** Roche thanked the Agency for the response and had no further comment.

#### Summary of CMC pre-NDA meeting

FDA noted the following comments conveyed to Hoffman-La Roche during the pre-NDA CMC meeting held on March 5, 2014:

- In order to support approval of drug manufactured at an alternate drug packaging site (Segrate, Italy), FDA stated that the NDA should contain at least three batches (from the new site) with three months accelerated stability data in NDA submission and up to three batches (from the new site) on long-term stability data reported in an annual report. The Agency stated that all stability update should be submitted within the first 60 days of the NDA submission.
- The NDA should contain acceptance criteria (b) (4) and a periodic evaluation strategy for microbiological tests.
- The NDA should contain the complete multipoint dissolution profile data for the pivotal clinical and registration stability batches both at release and on storage to support setting the final acceptance criterion.
- NDA should provide a clear overview of any formulation changes throughout development and the effects of these changes on dissolution performance and bioavailability, where appropriate.

FDA noted in section 14.10 of the briefing package, Roche stated that given the Fast Track Designation and rolling submission plans, Roche proposed to file one-month stability data from three batches of the cobimetinib Drug Product in the October, 2014, submission as part of the rolling NDA, and that three-month stability data would be provided for the same lots in December, 2014.

ADDITIONAL CMC COMMENTS:

13. Please refer to the following comment (response to question 2) included in the CMC meeting minutes dated March 12, 2014.

“No. The agency does not agree to your rational for excluding testing (b) (4) and periodic evaluation strategy for microbiological tests. Provide proposal for acceptance criterion (b) (4).”

**Company Response sent via email October 8, 2014:** Genentech acknowledges the above comment from the preliminary FDA responses for the March 5 CMC pre-NDA meeting. In the March 12 final FDA minutes, the Agency stated that “more data is required in order to determine whether it is acceptable (b) (4) Specification. Whether (b) (4) specification and microbiological tests can be omitted in the drug product specification, is a NDA review issue based on the information that will be provided in the NDA”. Based on this, in addition to content that was initially proposed, Genentech plans to include additional data on (b) (4) throughout manufacturing and stability which supports the proposal to (b) (4). Data available and presented in the NDA clearly demonstrates that (b) (4) a critical quality attribute for the cobimetinib drug product. We will also be providing the proposal and supporting rationale for the periodic evaluation strategy for microbiological tests.

**Discussion during the meeting:** Roche stated that they were ready to provide Module 3 and Module 4 earlier in the rolling submission.

Roche stated that they plan to submit data to support the request for omitting testing and to support the acceptance criterion (b) (4). FDA acknowledged this approach and will review the adequacy of this information during review of the NDA.

14. In the proposed NDA, provide the all information related to the manufacturing and testing sites which should include:
- Complete name and address of each facility
  - Contact information
  - Confirmation that all facilities are ready for FDA inspection

**Company Response sent via email October 8, 2014:**

- Module 3 of the NDA will include the complete name and address of each facility involved in the manufacturing and testing of cobimetinib.

- b. Contact information for the manufacturing and testing sites will be provided in Module 1 Section 1.1.2 (Form 356h), along with the names, addresses, FEI numbers, and the manufacturing steps and/or type of testing performed at the site.
- c. Genentech intends to ensure that all facilities are ready for FDA inspection as of December 11, 2014, the date of finalization of the NDA submission. With the initial component of the rolling submission to be submitted in October 2014, the Form 356h Box 29 will indicate that sites will be inspection ready on December 11, 2014. With the December submission, Genentech intends to provide the confirmation of inspection readiness. Is this consistent with Agency expectations?

**Discussion during the meeting:** FDA found Roche's proposals acceptable. Roche confirmed that drug substance and drug product manufacturing sites had an acceptable manufacturing history. Roche stated that the DP and DS manufacturing sites were inspected in March 2014, and the proposed packaging site in Segrate, Italy was inspected by the fall of 2013. In addition, Roche agreed to provide all of the manufacturing and testing sites for the drug product and drug substance in Module 3 of the NDA submission.

Roche agreed to work with FDA to schedule an application orientation meeting.

Roche stated that they intended to provide CMC information in October, 2014 submission, which would include 1-month stability data for drug product batches for commercial distribution packaged in Segrate, Italy, and that 3-month stability testing results would be provided in the final submission in December, 2014. In response to FDA's request for clarification, Genentech stated that although it was identified as an "alternative" packaging site, the Segrate site would be the sole packaging site for the commercial process. Genentech further confirmed that very limited data were available to support commercial drug product expiry dating. FDA noted that 3-month stability would be considered inadequate. FDA stated that an adequate package would include 6 month stability data using the commercial manufacturing process in real-time and accelerated testing. FDA stated that Roche should explore use of the packaging site for the NDA batches as part of the commercial manufacturing packaging site. Roche acknowledged FDA's comments.

**ADDITIONAL CLARIFICATION REQUESTED BY ROCHE:**

- A. Per the March 12, 2014 FDA minutes from the CMC pre-NDA meeting that stated that the Agency "will accept the stability information no later than 60 days after submission," Genentech intends to submit the stability update on December 11, 2014, the date of finalization of the NDA submission. Is this acceptable to the Agency?

**Discussion during meeting:** See discussion under FDA Additional Comment 14.

- B. On page 3 of the preliminary comments from the Agency, the Agency states that Genentech will be providing supportive safety data from studies (b) (4) :  
[REDACTED]

“Selected safety data will also be submitted from two ongoing trials [REDACTED] (b) (4) [REDACTED]”

On page 112 of the pre-NDA briefing package, under the company position for question 3, Genentech noted that data from Studies [REDACTED] (b) (4) will not be included in the SCS. Please refer to the text below:

“Of note, the Sponsor has made the following updates to what was proposed in the briefing package submitted in support of the Type C Content and Format Interaction (29 October 2013 as Serial Number 1146):

- Inclusion of additional detail from Study NO25395
- Adjustment to the proposed pooled dataset from Studies GO28141 and NO25395
- Inclusion of additional detail from Study MEK4592g
- Removal of ongoing combination studies [REDACTED] (b) (4) from the assessment of AESIs

Data from ongoing Studies [REDACTED] (b) (4) investigating the use of cobimetinib in combination with other agents (as detailed in Table 1) will not be included in the SCS because the safety profiles of the two different molecule combinations are dissimilar from the safety profile of cobimetinib plus vemurafenib and would not contribute to the risk profile of this combination.”

**Discussion during meeting:** No discussion occurred during the meeting.

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

Multidisciplinary:

- The content of a complete application was discussed.

Roche confirmed that they will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS will not be required for filing of an NDA; however, a determination of whether a REMS will be required for safe and effective use will be based on review of the data in the application
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Roche stated their intent to submit a complete application and therefore, there are no agreements for late submission of application components.

However, Roche stated that, based on the discussion captured under Additional Comment 14 (above), they may request submission of a late submission, i.e., within 30 days of the final component of the rolling NDA. This late component would contain 6-month real time

stability data to support approval of the sole commercial manufacturing and packaging site. Roche will contact FDA after further internal discussion to revisit this agreement

### **POST MEETING FOLLOW-UP:**

Roche submitted an amendment to IND 109307 on October 10, 2014, containing a proposal for rolling submission. In the proposal, Roche stated that they will submit all quality data in Module 3 in October, 2014, with one-month stability data for commercially-manufactured drug product. Roche will provide an update to Module 3 that includes 6-month stability data as a late submission of a minor component within 30 days of the NDA submission in December, 2014.

### **PREA REQUIREMENTS**

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

## **ISSUES REQUIRING FURTHER DISCUSSION**

- Please see action items below

## **ACTION ITEMS**

- Follow up with Roche regarding ocular toxicity
- Roche will follow up regarding submission of 6-month stability data within 30 days of submission of the last module of the NDA submission.

## **ATTACHMENTS AND HANDOUTS**

- There are no attachments or handouts

# MEETING ATTENDANCE LIST

Meeting between Hoffman-La Roche, Inc. and  
the Center for Drug Evaluation and Research.

DATE: October 8, 2014 TIME: 1:00 PM ROOM: WO 22; Rm 1313

NAME - Please print	AFFILIATION
Melanie Pierce	CDER / OHOP / DOP 2
Amarilis Vega	CDER / OSE / DRISK
Caryl Giuliano	CDRH / OIR / OGMIP
Devonne Hamilton-Stokes	CDER / OHOP / DOP 2
Rebecca Cohen	CDER / DOP 2
Anwar Gohreh	DHET / CDER
Monica Hughes	DOP 2 / CDER
Leah Her	DOP 2 / CDER
PATRICIA KEEGAN	DOP 2 / CDER
Sarah Wayson	Genentech
Edna Cho	Genentech
Lina Musib	Genentech
SUSAN ENG	Genentech
MIKA SOLAK	Genentech
ERIC HARTMAN	Genentech
Xian Zhou	Genentech
STEVE WACK	Genentech
Theodora Lambros	Genentech
Carmen Ladner	Genentech
Kavita Misty	Genentech
Jiyoung Chae	Genentech
Dou-Chung Chi	CDER / OHOP / DOP 2
DONNA BOSCOE	CDER / OIR / DUGP / MAB
Francois Fahnbuller	OSE
Lauren Jacano-Connor	OST

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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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MELANIE B PIERCE  
10/29/2014



IND 109307

**MEETING MINUTES**

Hoffman La-Roche, Inc.  
Attention: Lal Ninan, PhD  
Program Director, Pharma Technical Regulatory  
1 DNA Way, MS 241B  
South San Francisco, CA 94080-4990

Dear Dr. Ninan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zelboraf (vemurafenib) in combination with Cobimetinib (GDC-0973).

We also refer to the teleconference between representatives of your firm and the FDA on March 5, 2014. The purpose of the meeting was to discuss proposed CMC information that would impact the NDA submission.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

Ali H. Al Hakim, PhD  
Branch Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** CMC, Pre-NDA

**Meeting Date and Time:** March 5, 2014; 11:00AM-12:00PM (EST)  
**Meeting Location:** Teleconference

**Application Number:** IND 109307  
**Product Name:** Zelboraf (vemurafenib) in combination with Cobimetinib (GDC-0973)  
**Indication:** Treatment of Advanced Cancer  
**Sponsor/Applicant Name:** Hoffman La-Roche, Inc.

**Meeting Chair:** Ali Al Hakim, Branch Chief, ONDQA  
**Meeting Recorder:** Jewell Martin, Regulatory Project Manager, ONDQA

### FDA ATTENDEES

Ali Al Hakim, PhD, Branch Chief, ONDQA  
Liang Zhou, PhD, CMC Lead, ONDQA  
Robert Lu, PhD, CMC Reviewer, ONDQA  
Minerva Hughes, PhD, Biopharmaceutics, ONDQA  
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA

### SPONSOR ATTENDEES

Larry Cain, CMC Technical Regulatory (BSL)  
Peter Koettgen, CMC Drug Substance Chemistry (BSL)  
Caroline Maierhofer, CMC Drug Substance Analytics (BSL)  
Heidi Meier, CMC Technical Leader (BSL)  
Annie Miesch, CMC Drug Product Analytics (BSL)  
Kavita Mistry, CMC Technical Regulatory (BSL)  
Lal Ninan, CMC Technical Regulatory (SSF)  
Emmanuel Scheubel, CMC Drug Product Analytics (BSL)  
Sascha Schuster, CMC Technical Regulatory, silent note taker (BSL)  
Emily VanHassel, CMC Technical Regulatory, silent note taker (SSF)  
Peter Luetolf, incoming TDL and DP manufacturing, silent observer (BSL)

## 1.0 BACKGROUND

On December 20, 2013, Hoffman La-Roche, Inc. requested a Type B, Pre-NDA, CMC meeting to discuss proposed CMC information that would impact the future NDA submission. The Agency accepted this meeting as a Type B meeting and a Meeting Granted letter was sent on January 6, 2014. Meeting packages from Hoffman La-Roche, Inc. were received on January 31,

2014. On February 27, 2014, Hoffman La-Roche, Inc. requested that the meeting format be changed to a TCON and that the meeting discussion focus on Question 2 part 3 and Question 3.

## 2.0 DISCUSSION

### **Question 1: Drug Substance Control of Genotoxic Impurities**

Does the Agency agree with the Sponsor's control strategy for genotoxic impurities in the Drug Substance manufacturing process?

#### **FDA Response to Question 1:**

**Your control strategy is reasonable. However, the acceptance criteria and the details involved in the control steps are review-issues and will be evaluated during the NDA review process.**

#### **Discussion:**

**No further discussion required.**

### **Question 2: Drug Product Proposed Commercial Specification**

Does the Agency agree with the proposed commercial specification for cobimetinib 20 mg tablet? In particular, does the Agency agree with the Sponsor's proposal of  $Q = \frac{(b)}{(4)}\%$  at  $(b)(4)$  minutes as the dissolution release specification for the 20 mg tablet? Does the Agency agree with the Sponsor's rationale for excluding  $(b)(4)$  periodic evaluation strategy for microbiological tests?

#### **FDA Response to Question 2:**

- 1. Your proposed commercial specification for cobimetinib 20 mg tablet is reasonable. However, its adequacy is a review-issue (including the justification for type of impurities monitored during batch release and stability testing).**
- 2. The acceptability of the dissolution acceptance criterion is an NDA review issue. We recommend that you include in your NDA the complete multi-point dissolution profile data for the pivotal clinical and registration stability batches both at release and on storage to support setting the final acceptance criterion. In addition, the Biopharmaceutics section of your NDA should provide a clear overview of any formulation changes throughout development and the effects of these changes on dissolution performance and bioavailability, where appropriate. In general, the dissolution acceptance criterion should be set where  $Q = \frac{(b)}{(4)}\%$  occurs and based on the average data of 12 samples or stage 2 testing. A preliminary review of the data provided suggest that final sampling at 15 or 20 minutes may be more appropriate for your immediate release tablet and we encourage you to evaluate the applicability of 15 or 20 minute final sampling in your future NDA.**

- 3. No. The Agency does not agree to your rationale for excluding (b) (4) periodic evaluation strategy for microbiological tests. Provide proposal for acceptance criterion (b) (4).**

**Discussion:**

**Regarding Question 2, part 3, the Agency stated that more data is required in order to determine whether it is acceptable (b) (4) Specifications. Whether the (b) (4) microbiological tests can be omitted in drug product specification, is a NDA review issue based on the information that will be provided in the NDA.**

**Question 3: Change in Cobimetinib Drug Product Packaging Site and Market Application Stability Package**

Does the Agency agree with the Sponsor's plan to launch the commercial cobimetinib 20 mg tablets in bottles from an alternate Roche packaging site (e.g., Segrate [Italy]) based on 12 months of primary stability data generated on the registration batches from the Roche Kaiseraugst (Switzerland) packaging facility using identical packaging components and plans to demonstrate comparable packaging processes?

**FDA Response to Question 3:**

**Submit up to three batches (from the new site) with three months accelerated stability data in NDA submission and up to three batches (from the new site) on long-term stability data reported in annual report.**

**Discussion:**

**The Sponsor confirmed that the Segrate site is cGMP certified. The Sponsor expects that there will be no difference in the packing process between the sites. The Sponsor will provide 1 month of data from 3 batches put on manual filling at the time of the NDA filing. The Sponsor will provide 3 months of stability data during review of the NDA.**

**The Agency stated that any additional stability update should be submitted within the first 30 days of the NDA submission. The Sponsor stated that they will not be able to provide the information within that timeframe. The Agency stated that they will accept the stability information no later than 60 days after submission.**

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There are no specific issues requiring further discussion at this time.

### **4.0 ACTION ITEMS**

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

### **6.0 ATTACHMENTS AND HANDOUTS**

Handout provided by Hoffman La-Roche, Inc. on February 28, 2014, see attached.

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03/12/2014



IND 109307

**MEETING REQUEST-  
WRITTEN RESPONSES**

Hoffman La-Roche, Inc.  
Attention: Sarah Wayson, PhD  
Regulatory Program Management  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zelboraf (vemurafenib) and Cobimetinib (GDC-0973).

We also refer to your submission dated September 20, 2013, containing a Type C meeting request. The purpose of the requested meeting was to reach agreement on the proposed content and format of the NDA to support the proposed indication and enable full approval.

Further reference is made to our Meeting Granted letter dated October 11, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 30, 2013 background package.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Written Responses

APPEARS THIS WAY ON ORIGINAL



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**WRITTEN RESPONSES**

**Meeting Type:** Type C  
**Meeting Category:** Other  
**Application Number:** 109307  
**Product Name:** Vemurafenib (Zelboraf®) and Cobimetinib (GDC-0973)  
**Proposed Indication:** use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutations  
**Sponsor/Applicant Name:** Hoffman La-Roche, Inc.  
**Regulatory Pathway:** 505(b)(1)

**BACKGROUND**

On September 20, 2013, Roche requested a meeting to reach agreement on the proposed content and format of the NDA to support the proposed indication and enable full approval. Hoffman La-Roche also plans to request a pre-NDA meeting in Q3 2014 to acquaint the FDA with the results from the pivotal Phase 3 study and to resolve any pending data-driven issues regarding the analysis and presentation of the data.

On June 27, 2012, FDA and Roche participated in an End-of-Phase 1/Pre-Phase 3 meeting to discuss the major efficacy trial intended to support [REDACTED] (b) (4) for vemurafenib, in combination with GDC-0973, and to support an original NDA for GDC-0973 for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation [REDACTED] (b) (4). Key issues included FDA agreement to a randomized, double-blind placebo controlled study design but recommended an independent review of PFS in addition to investigator assessments; FDA recommendation that the final OS analysis should be sufficiently powered; FDA inability to determine if the selected dose and dosing regimen is appropriate; and, FDA recommended additional safety assessments.

Vemurafenib is a BRAF inhibitor that blocks the function of the V600E-mutated BRAF protein and is FDA-approved as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA approved test.

Cobimetinib GDC-0973 is an investigational MEK inhibitor that Roche states has shown anti-tumor activity in multiple xenograft models that harbor mutations for BRAF or KRAS inhibits the phosphorylation of ERK1/2 and also inhibits proliferation in a panel of cell lines harboring either wild-type or mutant KRAS and/or BRAF.

The dosage form for vemurafenib and cobimetinib is a film-coated immediate-release tablet; the route of administration is oral.

## OVERVIEW OF CLINICAL STUDIES OF COMETINIB SUPPORTING THE NDA

### Pivotal Trial GO28141 (COBRIM):

The GO28141 (coBRIM) trial is a randomized, double-blinded, placebo-controlled, phase 3 trial in 500 patients with previously untreated BRAFV600-mutation positive unresectable or metastatic melanoma. Randomization will be stratified by geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c) (yes vs. no). Eligible patients will be randomly assigned in a 1:1 ratio to two treatment arms:

- Experimental arm: vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib (GDC-0973) 60 mg PO QD on Days 1–21 of each 28-day treatment cycle
- Control arm: vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1–28 and placebo PO once daily (QD) on Days 1–21 of each 28-day treatment cycle

Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest. Patients on the vemurafenib and placebo treatment arm will not be eligible to cross over to the vemurafenib and cobimetinib (GDC-0973) treatment arm at disease progression and will be followed for survival.

The primary endpoint is PFS as assessed by investigator in 8-week intervals according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Assuming that the median PFS is 5 months in the vemurafenib plus placebo arm and 11 months in the vemurafenib plus cobimetinib arm, a total of 206 events are needed to detect a hazard ratio of 0.55 with 95% power at a 2-sided alpha level of 5%. The primary analysis will be a stratified log-rank test performed on the ITT population.

The trial is also designed to test OS. Assuming that the median OS is 15 months in the vemurafenib plus placebo arm and 20 months in the vemurafenib plus cobimetinib arm, a total of 385 events are needed to detect a hazard ratio of 0.75 with 80% power at a 1-sided alpha level of 2.5%. Two interim analyses will be performed, one at the final PFS analysis and another after 256 (67%) events. The OBF boundary method is utilized with respective alpha allocations of 0.000085 and 0.012; the alpha for the final analysis is 0.0463.

Other major secondary endpoints include best overall response rate (BORR). A hierarchical procedure is proposed to adjust for multiplicity in testing the order of the secondary endpoints of BORR and OS.

### Supportive Trials:

For the NDA submission, Hoffman La Roche plans to submit supportive trials. Trial NO25395 (BRIM7) will provide efficacy and safety data on the combination of cobimetinib and vemurafenib. Trial MEK4592g will provide safety data cobimetinib. Selected safety data will also be submitted from two ongoing trials (b) (4).

## Sponsor Submitted Questions and FDA Response:

### FDA INTRODUCTORY COMMENT:

The purpose of these Written Responses is to provide general technical comments and recommendations on the format and content of a planned NDA to support the proposed indication:

“cobimetinib is indicated for use in combination with Vemurafenib for the treatment of patients with unresectable or Metastatic melanoma with BRAF v600 mutations.”

FDA responses to the following questions, as well as any additional FDA comments, do not constitute an agreement on the format and content of a complete application under PDUFA V. FDA advises Hoffman La-Roche to submit a request for a Type B, pre-NDA meeting for Roche and FDA to discuss and reach agreement on the content of a complete application for the above proposed indication—if Roche decides to submit an NDA after its review of the results of trial GO21841.

### CLINICAL/STATISTICAL:

1. Does the Agency agree with the proposed presentation of the statistical analysis of efficacy and safety for the pivotal study GO28141 (coBRIM), as described in the Statistical Analysis Plan?

**FDA Response:** No. The analysis population for best overall response rate (BORR), defined as patients in the Intention to treat (ITT) population who were randomized at least 18 weeks before the data cutoff date, is not acceptable because it violates the ITT principle. In order to include information on objective responses in product labeling or promotional materials, the primary analysis of overall response rate must be conducted in the ITT population which consists of all randomized patients and has been confirmed to be durable for at least 4 weeks.

2. Does the Agency agree with the planned analyses and presentation of safety data in the Summary of Clinical Safety (SCS) and the Integrated Summary of Safety (ISS)?

**FDA Response:** The planned analyses appear reasonable. However, the NDA Table of Contents in the meeting package does not identify the placement of the datasets and analyses. The NDA submission must include datasets and analyses of the major efficacy trial and all supportive studies. Tabulation and Analyses Datasets must be included in 5.3.5.3.

With regard to the presentation of safety data we note the following deficiencies:

- Please note that the absence of a complete Integrated Summary of Safety (ISS) can result in a determination that the application is incomplete.
- Adverse Events of Special Interest (AESI) should also include secondary malignancies. Safety data proposed from the supportive ongoing studies should include all the AESIs identified. The proposed AESIs listed in the section on

adverse events are not consistent with the selected analyses proposed throughout the meeting package. Provide a list of the AESIs to be included in the Summary of Clinical Safety for review and agreement by the FDA prior to the NDA submission.

FDA also has the following recommendation for data presentation:

- Although not a requirement, FDA recommends that an Overview of Safety section (2.5.5) be included in the Clinical Overview (2.5).

For details, refer to Guidance for Industry: Integrated Summaries for Effectiveness and Safety: Location Within the Common Technical Document, located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>.

3. Does the Agency agree with the proposed contents of the Summary of Clinical Efficacy (SCE) and the proposal not to include an Integrated Summary of Efficacy (ISE)?

**FDA Response:** No. Per 21 CFR 314.50 (d)(5)(v), an Integrated Summary of Efficacy (ISE) must be included in the NDA submission. The ISE must be placed in Module 5, section 5.3.5.3. The NDA submission must include datasets and analyses of the pivotal trial and all supportive studies. Tabulation and Analyses Datasets must be included in 5.3.5.3. Absence of the ISE can result in a determination that the application is incomplete and may result in a refusal-to-file action.

Although not a requirement, FDA recommends that an Overview of Efficacy section (2.5.4) be included in the Clinical Overview (2.5).

For details, refer to Guidance for Industry: Integrated Summaries for Effectiveness and Safety: Location Within the Common Technical Document, located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>.

4. Does the Agency agree with the proposed plan for submitting patient narratives?

**FDA Response:** The proposed plan appears reasonable. However, the NDA Table of Contents in the meeting package does not identify the placement of the narratives. Narratives must be included in the NDA submission. FDA requests that the clinical study reports and summaries contain hyperlinks to the case narratives. Additional narratives and documentation may be requested during the NDA review.

5. Does the Agency agree with the proposed submission of Case Report Forms (CRFs)?

**FDA Response:** An annotated Case Report Form (CRF) must be included in the NDA submission with hyperlinks provided to the define file for specific data variables.

6. Does the Agency agree with the proposed plan for submitting Clinical Study Reports (CSRs)?

**FDA Response:** The proposed plan appears reasonable.

7. Does the Agency agree with the proposed contents and format of the datasets?

**FDA Response:** FDA agrees with the proposed format of CDISC data.

There is insufficient detail in the meeting package regarding the contents of the datasets. FDA recommends SDTM datasets. Data Tabulation and Data Analyses Datasets should be provided with raw and derived datasets.

At the time of the pre-NDA meeting, please confirm that the following will be provided in the NDA submission:

- A reviewer's guide
- A define file

For details, refer to FDA Draft Guidance for Industry, "Providing Regulatory Submissions in Electronic Format- Standardized Study Data" located at <http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf>

8. Does the Agency agree with the proposed statistical programs to be included?

**FDA Response:** Yes.

9. Does the Agency agree with the proposed plan to provide radiographic images only upon request?

**FDA Response:** The proposed plan appears reasonable.

#### CLINICAL PHARMACOLOGY:

10. Is the planned format of the clinical pharmacology data in support of the NDA acceptable to the Agency?

**FDA Response:** The planned format and content of the clinical pharmacology plan as described in Section 12.6 appears generally acceptable to support the proposed NDA for cobimetinib in combination with vemurafenib. The NDA should also include an assessment of the potential pharmacokinetic (PK) interaction between cobimetinib and vemurafenib in the proposed combination therapy via cross-arm comparisons and cross-study comparisons.

In the NDA submission, include the physiologically-based pharmacokinetic (PBPK) report that is intended to predict the effect of a strong CYP3A inducer on cobimetinib

pharmacokinetics and help determine the need for a drug interaction trial with a strong CYP3A inducer. Additional clinical pharmacology studies (e.g., drug interaction study with a strong CYP3A inducer, dedicated drug interaction study of cobimetinib in combination with vemurafenib) may be requested after review of the NDA.

In the NDA submission, provide a description of the hepatic impairment study and drug interaction study with itraconazole as postmarketing requirements (PMRs), including major milestones (e.g., study completion date, submission of final study report).

In the NDA submission, address the following clinical pharmacology related questions in the Summary of Clinical Pharmacology Studies (2.7.2):

- a. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
- b. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
- c. What are the exposure-response relationships (dose-response, exposure-response) for safety?
- d. How is the QT prolongation potential of cobimetinib assessed? What are the conclusions and proposed labeling description?
- e. What are the characteristics of absorption, distribution, metabolism, and excretion of cobimetinib?
- f. What are the effects of food on the bioavailability of cobimetinib, and dosing recommendation with regard to meals and meal types?
- g. What influence do the intrinsic factors (as listed below but not limited to) have on cobimetinib exposure and/or its pharmacodynamic responses? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
  - (1) Gender
  - (2) Race
  - (3) Weight
  - (4) Disease
  - (5) genetic polymorphism
  - (6) hepatic impairment
  - (7) renal impairment

- h. What influence do the extrinsic factors (as listed below but not limited to) have on cobimetinib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
- (1) concomitant medications
  - (2) CYP and/or transporter based drug-drug interactions
  - (3) drug-drug interactions with pH-elevating agents
  - (4) diet
  - (5) smoking

Regarding the format and content related to clinical pharmacology sections of the NDA submission:

- a. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.
- b. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK or pharmacodynamics (PD). For example, domains related to safety (e.g., adverse events), demographics, non-PK laboratory values and concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.
- c. Provide all concentration-time and derived PK parameter datasets as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- d. Present the PK parameter data as geometric mean with coefficient of variation (and mean  $\pm$  standard deviation) and median with range as appropriate in the study reports.
- e. Provide a table listing of patients with renal or hepatic impairment who have received cobimetinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLcr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, total bilirubin, etc. for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.
- f. Submit the following datasets to support the population PK analysis:
  - (1) SAS transport files (\*.xpt) for all datasets used for model development and validation.

- (2) Description of each data item provided in a Define.pdf file (any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets).
  - (3) Model codes or control streams and output listings for all major model building steps, (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with \*.txt extension (e.g., myfile\_ctl.txt, myfile\_out.txt).
  - (4) Model development decision tree and/or table which gives an overview of modeling steps.
- g. For the population analysis reports, submit:
- (1) Standard model diagnostic plots.
  - (2) Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line.
  - (3) Model parameter names and units in tables (e.g., oral clearance should be presented as CL/F (L/h) and not as THETA(1)).
  - (4) Summary of the report describing the clinical application of modeling results.

For more information, refer to the following pharmacometric data and models submission guidelines at

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

- h. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships and include the results of this exploratory analysis in the NDA submission.

For more information, refer to the FDA Guidance for Industry found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

- i. Submit the following items for QTc study/assessment:
- (1) Copy of the QT/QTc study protocol.
  - (2) Copy of the Investigator's Brochure.
  - (3) Annotated CRF.
  - (4) Define file which describes the contents of the electronic data sets.
  - (5) Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses.

- (6) ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com)).
- (7) Completed Highlights of Clinical Pharmacology Table.

11. Does the Agency agree with the proposal to conduct the hepatic impairment study in healthy subjects?

**FDA Response:** The proposal to conduct the hepatic impairment study in healthy subjects appears reasonable. However, the study may not be considered adequate until evaluable data from at least 6 subjects in each arm, mild, moderate and severe hepatic impairment, are obtained and submitted. If a clinically important increase in cobimetinib exposure is observed in subjects with mild or moderate hepatic impairment, the proposed dose of 20 mg should be reduced in subjects with severe hepatic impairment.

#### REGULATORY

12. Is the collection and organization of supporting documentation for the overall Table of Contents of the NDA acceptable?

**FDA Response:** No. See FDA responses to Questions 2, 3, 4, 5, and 7.

13. Does the Agency agree with the proposed timing and plan for the submission of a Pediatric Study Plan?

**FDA Response:** The proposed plan to submit a request for orphan drug designation appears reasonable. However, Roche must provide evidence that orphan drug designation has been granted to cobimetinib for the proposed indication or submit an adequate initial pediatric study plan (iPSP). Please note that an iPSP would be inadequate if it states that a Sponsor *intends* to request orphan drug designation and does not provide an outline of the pediatric study or studies that the sponsor plans to conduct or, if applicable, a request for a deferral, partial waiver, or waiver, including the grounds for requesting a waiver or deferral.

Please refer to FDA Guidance for Industry “Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans” which can be accessed at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/UCM360933.pdf>.

14. Does the Agency agree with the proposal not to submit a Risk Evaluation and Mitigation Strategy (REMS) for the use of cobimetinib in the proposed indication?

**FDA Response:** The question is premature as there is insufficient safety data provided in the meeting package. FDA is unable to determine if a REMS would be necessary to ensure that the benefits of the drug outweigh its risks.

## **PREA REQUIREMENTS**

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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/s/  
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MELANIE B PIERCE  
11/29/2013



IND 109307

**MEETING REQUEST-  
WRITTEN RESPONSES**

Hoffman-La Roche, Inc.  
Attention: Irene Figari  
Regulatory Program Management  
1 DNA Way  
South San Francisco, CA 94080

Dear Ms. Figari:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zelboraf (vemurafenib), in combination with GDC-0973”.

We also refer to your submission dated February 6, 2013, containing a Type C meeting request. The purpose of the requested meeting was to confirm the suitability of our planning for clinical pharmacology studies intended to support the use of GDC-0973 in New Drug Applications including for initially the use of GDC-0973 in combination with Vemurafenib

Further reference is made to our Meeting Granted letter dated March 1, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 21, 2013 background package.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager at (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

IND 109307  
Page 2

Enclosure:  
Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**WRITTEN RESPONSES**

**Meeting Type:** Type C  
**Meeting Category:** Other

**Application Number:** IND 109307  
**Product Name:** Zelboraf (vemurafenib, in combination with (GDC-0973))  
**Indication:** treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by a U.S. Food and Drug Administration (FDA)–approved test.

**Sponsor/Applicant Name:** Hoffman-LaRoche, Inc.  
**Regulatory Pathway:** 505(b)(1)

**BACKGROUND**

Meeting History:

On June 27, 2012, FDA and Hoffman-La Roche, Inc., had an End-of-Phase 1/Pre-Phase 3 meeting to discuss the proposed development plan to support the use of GDC-0973 in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutations and to obtain the Agency's feedback on the appropriate regulatory strategy for vemurafenib and GDC-0973.

On November 27, 2012 a meeting was held between FDA and Hoffman-La Roche to discuss End-of-Phase 2 data Chemistry, Manufacturing, and Controls (CMC) data and to obtain the Agency's feedback on Genentech/Roche's proposals for the technical development of GDC-0973 in preparation for the future NDA submission.

On February 7, 2013, Hoffman-LaRoche, Inc., requested a meeting to confirm the suitability of planned clinical pharmacology studies intended to support the use of GDC-0973 in combination with Vemurafenib.

Chemical Description

GDC-0973 is a highly specific inhibitor of MEK1/2. (GDC-0973) is a 20-mg film-coated immediate-release tablet for oral administration. The 20-mg tablets (b)(4). The excipients in the formulation (lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate) and the ingredients in the film coating (polyvinyl alcohol (b)(4), titanium dioxide, polyethylene glycol 3350, and talc) are commonly used in solid oral dosage formulations and are of compendial quality.

Written Response

GDC-0973 (mitogen-activated protein kinase/extracellular signal-regulated kinase [MEK] inhibitor) is being investigated as a single agent under US IND [REDACTED] (b) (4) [REDACTED].

GDC-0973 is currently being evaluated in Phase 1 studies. An ongoing Phase 3 trial (Study GO28141) in previously untreated BRAFV600 mutation–positive patients with unresectable locally advanced or metastatic melanoma will provide the clinical data to support an initial market application for GDC-0973 in combination with vemurafenib (IND 109,307).

Zelboraf (vemurafinib) is an FDA-approved B-Raf enzyme inhibitor indicated for the treatment of patients with late-stage melanoma that is V600E mutation positive. Vemurafenib interrupts the B-Raf/MEK step on the B-Raf/MEK/ERK pathway.

The recommended dosing regimen of GDC-0973 tablets is 60 mg taken orally on Days 1-21 of each 28-day treatment cycle, in combination with vemurafenib tablets (960 mg taken orally twice daily).

Proposed Clinical Pharmacology Plan:

The clinical pharmacology of GDC-0973 was investigated in several Phase 1 clinical pharmacology studies to assess single- and multiple-dose pharmacokinetics (PK), relative bioavailability (BA) and food effect, absolute BA, mass balance and metabolism profile, drug-drug interaction (DDI) potential, and QT prolongation potential. These studies and assessments are conducted in patients with solid tumors and in healthy subjects. A hepatic impairment study in cancer patients and effect of CYP3A inhibitor on the PK of GDC-0973 in healthy subjects will be conducted. Population PK (PopPK) modeling will be utilized to assess the potential sources of PK variability and the behavior of the compound in special populations and to evaluate PK/PD relationships for efficacy and safety, including exposure-response, where appropriate.

Clinical Studies to Support the Clinical Pharmacology and Biopharmaceutics of GDC-0973**Table 1 Studies Supporting the Clinical Pharmacology and Biopharmaceutics of GDC-0973**

Study Number (Number of Subjects)	Phase	Objectives	Study Design	Population	Dosing Regimen	Status
MEK4592g (n=97)	1a	Stage I, IA, II, IIA: To characterize the safety and single- and multiple-dose pharmacokinetics of GDC-0973 and assess QT interval prolongation potential	Multicenter, non-randomized, open-label, dose-escalation study	Patients with solid tumors	Stages I, II: 0.05, 0.10, 0.20 mg/kg QD and 10, 20, 40, 60, 80 mg QD on 21/7 day schedule Stages IA, IIA: 60, 80, 100, 125 mg QD on 14/14 day schedule	C
MEK4592g (n=15)	1a	Stage III: To evaluate the effect of GDC-0973 on the pharmacokinetics of midazolam and dextromethorphan	Multicenter, two-period, non-randomized, sequential study	Patients with solid tumors	GDC-0973: 60 mg QD on 21/7-day schedule starting on Day 3 Midazolam: Single 2-mg oral dose on Days 1 and 15 Dextromethorphan: Single 30-mg oral dose on Days 1 and 15	O Last Protocol Amendment 7 submitted on 12 December 2012 SN0275 to IND (b) (4)
NO25395 (N=125)	1b	Stage I, II: To evaluate the safety, tolerability, and pharmacokinetics of the vemurafenib and GDC-0973 combination	Multicenter, non-randomized, open-label, dose-escalation study	Patients with locally advanced/ unresectable or metastatic melanoma	Stage I: GDC-0973 60, 80, 100 mg QD on 14/14 day schedule and vemurafenib 720, 960 mg BID Stage II: GDC-0973 60 mg QD on 21/7 and 28/0 day schedule and vemurafenib 720, 960 mg BID	O Protocol Amendment F submitted on 18 July 2012 as SN0568 to IND 109,307
MEK4952g (n=12)	1	To characterize the absolute bioavailability of GDC-0973	Single-dose, open-label, sequential, crossover study	Healthy subjects	GDC-0973: Single 2-mg IV infusion over 30 min and single 20-mg oral dose (4x5-mg capsules)	C CSR submitted: IND 109,307 SN0220

**Table 1 Studies Supporting the Clinical Pharmacology and Biopharmaceutics of GDC-0973 (cont.)**

Study Number (Number of Subjects)	Phase	Objectives	Study Design	Population	Dosing Regimen	Status
MEK4953g (n=20)	1	To assess the relative bioavailability of GDC-0973 capsule and tablet and evaluate the effect of food on GDC-0973 pharmacokinetics	Single-dose, randomized, open-label, crossover study	Healthy subjects	GDC-0973: Single 20-mg tablet dose (fasted state or with high-fat meal); single 20-mg capsule dose (4x5 mg, fasted)	C CSR submitted: IND 109,307 SN0220
MEK4954g (n=20)	1	To evaluate the effect of a proton pump inhibitor (rabeprazole) on GDC-0973 pharmacokinetics in the presence and absence of a high-fat meal	Single-dose, randomized, open-label, crossover study	Healthy subjects	GDC-0973: Single 20- mg tablet dose (fasted state or with high-fat meal) Rabeprazole: 20-mg dose QD x5 days	C CSR submitted: IND 109,307 SN0220
GP28369 (n=6)	1	To characterize the mass balance and metabolite profile of GDC-0973	Single-dose, open-label study	Healthy subjects	GDC-0973: Single 20-mg oral solution dose of GDC-0973 with <sup>14</sup> C-GDC-0973 (200 µCi)	C, R
TBD (n=12)	1	To evaluate the effect of a potent CYP3A inhibitor (itraconazole) on GDC-0973 pharmacokinetics	Single-dose, randomized, open-label, fixed-sequence, two-period study	Healthy subjects	GDC-0973: Single 10-mg tablet dose on Days 1 and 18 Itraconazole: 200 mg on Days 15-28	P
TBD (n=16)	1	To characterize the pharmacokinetics of GDC-0973 in cancer patients with hepatic impairment	Single-dose, open-label study	Cancer patients	GDC-0973: 60 mg QD on 14/7 day schedule	P

BID=twice a day; C=completed; CYP=cytochrome P450; IV=intravenous; O=ongoing; P=planned; QD=once-daily, QT=time between start of the Q wave and end of the T wave; R=Reporting; TBD=to be determined.

## Written Response

As of 30 January 2013, the PK of GDC-0973 administered as a single agent has been characterized in 115 patients with solid tumors in a Phase 1a study and in 58 healthy subjects in four clinical pharmacology studies. The PK of GDC-0973 and vemurafenib administered in combination has been assessed in 71 patients with melanoma in a Phase 1b study (data cutoff: July 2012).

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**Sponsor Submitted Questions and FDA Response:****CLINICAL PHARMACOLOGY:**

1. Does the FDA agree that the conducted and planned clinical pharmacology studies for GDC-0973 are appropriate and sufficient to support the metastatic melanoma indication?
  - a. List of clinical pharmacology studies already conducted:
    - (1) Absolute BA study in healthy subjects
    - (2) Relative BA and food effect study in healthy subjects
    - (3) Effect of PPI on GDC-0973 pharmacokinetics in healthy subjects
    - (4) Effect of GDC-0973 on CYP3A substrate (midazolam) and CYP2D6 substrate (dextromethorphan) in cancer patients
    - (5) Human mass balance study in healthy subjects
  - b. Planned clinical pharmacology studies:
    - (1) Effect of CYP3A inhibitor (itraconazole) on GDC-0973 in healthy subjects
    - (2) Hepatic impairment study in cancer patients

**FDA Responses:** The conducted and planned clinical pharmacology studies appear appropriate. However, the adequacy of these studies to support the metastatic melanoma indication will be determined upon review of the to-be-submitted NDA

2. Does the FDA agree with the proposed study design for the CYP3A inhibition study using itraconazole as the probe inhibitor?

**FDA Responses:** Yes. The proposed study design for the CYP3A inhibition study using itraconazole as the probe inhibitor appears acceptable.

3. A CYP3A inducer study (with rifampin) will be conducted only if the results of the CYP3A inhibitor (itraconazole) study on GDC-0973 show a significant role for CYP3A in the metabolism of GDC-0973. Does the FDA agree?

**FDA Responses:** The proposal to stage the drug-drug interaction studies using PBPK modeling and simulation appears acceptable. The physiological-based pharmacokinetic (PBPK) model of GDC-0973 should be verified and updated using results from itraconazole trial to predict the effect of a strong CYP3A inducer. The need to conduct a

## Written Response

CYP3A inducer clinical study (with rifampin) will be determined when this information becomes available.

4. Does the FDA agree that no additional DDI studies are required beyond the conducted and planned DDI studies to support the metastatic melanoma indication?

**FDA Responses:** No. See FDA's answer to question 3. In addition, adequately assess the potential for a pharmacokinetic interaction between GDC-0973 and vemurafenib. Furthermore, provide sufficient justification in the to-be-submitted NDA if there is no plan to conduct drug-drug interaction trials with regard to OATP and OCT drug transporters. Refer to the Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

5. Does the FDA agree with proposed study design for the hepatic impairment study? Furthermore, does the FDA agree with the submission of the completed hepatic impairment study as a post-approval commitment for the metastatic melanoma indication?

**FDA Responses:** With regard to study design, as GDC-0973 is a substrate of CYP3A4, the protocol for hepatic impairment trial should specify that strong CYP3A4 inhibitors (including grapefruit juice) and strong CYP3A inducers (including St. John's wort or hyperforin) should be avoided. A list of such drugs should be included in the protocol. Submit the final protocol for FDA review before initiation of the trial.

With regard to timing of the study report submission, FDA recommends including the final study results in the initial NDA submission. A post-marketing requirement (PMR) for the hepatic impairment study with proposed submission timeline could be considered if this study is not completed at the time of the NDA submission.

6. Does the FDA agree that a renal impairment study is not necessary to support the metastatic melanoma indication?

**FDA Responses:** FDA recommends that Roche explore the renal function parameters (such as SCr, CLcr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD) as covariates on the pharmacokinetics of GDC-0973 in the population pharmacokinetic analyses. The need to conduct a dedicated renal impairment trial with GDC-0973 will be determined during review of the to-be-submitted NDA.

7. In the relative BA and food effect study using the prototype tablets, no effect of food was seen on GDC-0973 pharmacokinetics. Optimized tablets, which are similar to the prototype tablets in composition and manufacture, will be used in Phase 3 and for commercialization (reviewed by the Agency as part of the Briefing Package for the CMC End of Phase 2 meeting [27 November 2012]). Given that no food effect was seen with

Written Response

the prototype tablets, we propose that a second food-effect study using the optimized tablets is not necessary. Does the FDA agree?

**FDA Responses:** It appears that a second food-effect study using the optimized tablets may not be necessary; however, final determination will be made during the review of the to-be-submitted NDA.

8. Does the FDA agree with the proposed PopPK and E-R analyses plans?

**FDA Response:** In principle, the proposed Pop PK and exposure-response analysis plans appear acceptable, but there is limited information included in the briefing package for FDA to provide any specific comments. FDA recommends Roche resubmit these analysis plans with more specific details for FDA review prior to initiation of the proposed phase 3 trial.

### **PREA REQUIREMENTS**

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

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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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MELANIE B PIERCE  
04/22/2013



IND 109307

**MEETING MINUTES**

Hoffman-La Roche, Inc. c/o  
Genentech, Inc.  
Attention: Lal Ninan, PhD  
Manager, Pharma Technical Regulatory  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Ninan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0973 (XL518) in combination with Zelboraf™ (vemurafenib) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on November 27, 2012. The purpose of the meeting was to obtain the Agency's feedback on Genentech/Roche's proposals for the technical development of GDC-0973 in preparation for the future NDA submission.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2072.

Sincerely,

*{See appended electronic signature page}*

Jewell D. Martin, MA, MBA, PMP  
Regulatory Project Manager for Product Quality  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** CMC, End of Phase 2

**Meeting Date and Time:** November 27, 2012, 10:00AM -11:00AM (EST)  
**Meeting Location:** Teleconference

**Application Number:** IND 109307  
**Product Name:** GDC-0973 (XL518) in combination with Zelboraf™  
(vemurafenib) tablets  
**Indication:** For the Treatment of Advanced Cancer  
**Sponsor/Applicant Name:** Hoffman-La Roche, Inc./Genentech

**Meeting Chair:** Jewell Martin, Regulatory Project Manager  
**Meeting Recorder:** Nallaperumal Chidambaram, PhD, Acting Branch Chief

**FDA ATTENDEES**

Nallaperumal Chidambaram, PhD, Acting Branch Chief, ONDQA  
Sue Ching Lin, PhD, CMC Reviewer, ONDQA  
Kareen Riviere, PhD, Biopharmaceutics Reviewer, ONDQA  
Suzanne Demko, Clinical Team Leader, DOP2  
Jian Wang, Ph.D, Clinical Pharmacology Reviewer, OCP  
Hong Zhao, Ph.D, Clinical Pharmacology Team Leader, OCP  
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA

**SPONSOR ATTENDEES**

Mark Dresser, Clinical Pharmacology  
Nicole Kaiser, CMC Technical Regulatory  
Sanjeev Kothari, Pharmaceutical Sciences  
Alexander Maurer, CMC Drug Product Formulation  
Heidi Meier, CMC Technical Leader  
Luna Musib, Clinical Pharmacology  
Lal Ninan, CMC Technical Regulatory  
Ramani Raghavan, CMC Technical Regulatory  
Emmanuel Scheubel, CMC Drug Product Analytics  
TG Venkateshwaran, CMC Technical Regulatory

## 1.0 BACKGROUND

In a letter dated September 26, 2012, received by the Agency on September 27, 2012, Genentech/Roche requested a Type B, End-of-Phase 2 (EOP 2), Chemistry, Manufacturing, and Controls (CMC) meeting to obtain the Agency's feedback on Genentech/Roche's proposals for the technical development of GDC-0973 in preparation for the future NDA submission. The Office of New Drug Quality Assessment (ONDQA) issued a Meeting Granted letter to Genentech/Roche on October 17, 2012. Genentech/Roche submitted their meeting background package on October 26, 2012, received by the Agency on October 31, 2012. The Agency provided meeting preliminary comments on November 16, 2012. On November 19, 2012 Genentech/Roche provided additional information regarding Question 3; the Agency provided a response on November 21, 2012. Genentech/Roche requested to change the meeting format from a face-to-face meeting to a teleconference on November 21, 2012 and provided a response to the Agency's request for additional information on November 26, 2012.

## 2.0 DISCUSSION

### Drug Substance Starting Material Strategy

#### Question 1(a):

Does the Agency agree with the Sponsor's rationale and justification for the designation of the following compounds as the API starting materials for the commercial manufacture of GDC-0973?

[REDACTED] (b) (4)

#### FDA Response to Question 1(a):

- Your proposal to designate the above (b) (4) compounds as starting materials is reasonable based on the information you included in the briefing package. However, the final determination will be made at the time of NDA review based on the totality of data submitted (see bullets below).
- Evaluate genotoxic risk for starting materials, for example, [REDACTED] (b) (4). If a compound is found to be genotoxic, set specification to that associated with a potential daily impurity exposure supported by compound-specific risk assessment. Genotoxic risk for any starting material as well as downstream impurities that may result from starting materials needs to be addressed at a pre-NDA meeting.
- In the original NDA, submit the following information for all proposed starting materials. This information will be reviewed for adequacy at the time of NDA submission:

- **A detailed synthetic scheme.**
- **Appropriate controls of the proposed starting materials using validated analytical test methods to separate and measure potential impurities, including chiral impurities.**
- **A thorough discussion of potential carry-over of impurities that are present in the starting materials to the final drug substance, based on analytical data.**
- **Data from purging studies to demonstrate that the impurities in the proposed starting materials, when spiked at levels equivalent to or higher than the proposed limits in the starting materials, will be effectively removed during the drug substance manufacturing process.**
- **Full supplier information from the intended vendors of the proposed starting materials.**
- **Acceptable change control strategies for any potential revisions to the manufacture of the proposed starting materials, including the proposed procedures for the vendor's reporting of any changes in starting material manufacture to you.**
- **Ensure that the analytical methodology used for the drug substance is capable of resolving and quantifying impurities carried over from the proposed starting materials as well as any process impurities that may result from the synthesis of the drug substance from the proposed starting materials. Provide these data to support your conclusions.**
- **Maintain highly purified and well characterized reference starting materials and establish the stability of the starting materials.**
- **Detailed justifications for the starting materials, including those outlined in the background packages, in the NDA submission.**
- **Supportive literature data, as available.**

Discussion:

No further discussion required.

**Question 1(b):**

Does the Agency agree with the proposal to designate (b) (4) for the manufacture of GDC-0973 based on the guidance provided in ICH Q11?

**FDA Response to Question 1(b):**

**Yes, we agree that (b) (4) the manufacture of GDC-0973 based on ICH Q11. However, ensure the specification (b) (4) meets USP/NF requirements, (b) (4) potential impurities, including geometric isomeric impurities, need to be controlled.**

Discussion:

No further discussion required.

**Question 2:**

Does the Agency agree that the dissolution method proposed, USP Apparatus 2 paddle; rotation speed 50 rpm with a medium of 0.05M acetate buffer pH 4.5, is adequate for quality control testing of the GDC-0973 20 mg film-coated tablet registration (primary stability) batches, both for release and stability. Does the agency agree that the same

proposed dissolution method, USP Apparatus 2 paddle; rotation speed 50 rpm with a medium of 0.05M acetate buffer pH 4.5 is also adequate for commercial drug product testing, both for release and stability?

**FDA Response to Question 2:**

**The proposed dissolution method appears adequate for quality control testing of the registration batches and commercial drug product for release and on stability. Include in your NDA submission the complete dissolution report with the following information:**

- a. **Solubility data for the drug substance covering the pH range;**
- b. **Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;**
- c. **Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);**
- d. **Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm$  10-20% change to the specification-ranges of these variables);**
- e. **Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**

**Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA.**

Discussion:

No further discussion required.

**Question 3:**

Based on in-vivo and in-vitro results, no further clinical studies are planned in order to bridge the GDC-0973 PiC and optimized tablet formulation. The GDC-0973 optimized 20 mg tablet formulation will be used in Phase 3 clinical studies and is the same as intended for commercial approval. Does the Agency agree with this proposal?

**FDA Response to Question 3:**

**There is insufficient data/information to answer this question. Provide a head-to-head qualitative and quantitative comparison in table format of the formulation composition**

**and manufacturing process for the GDC-0973 PiC prototype tablets and the GDC-0973 optimized tablets. Please clearly indicate the differences between the prototype and the optimized products. Note that major changes may require additional supporting data beyond dissolution profiles comparisons (e.g. BA/BE studies).**

**Genentech/Roche (sponsor) provided attachment on 11/19/2012 as a follow up response to question #3 – See Section 5.0 attachment**

**Comment sent by Agency to Sponsor on 11/21/2012:**

Provide your proposal for the "PK/Clinical/CMC" studies that you are planning to conduct with the optimized formulation. Additionally, indicate what previous information "PK/Clinical/CMC" you would like to leverage by bridging the prototype and optimized formulations.

**Genentech/Roche (sponsor) response provided on 11/26/2012:**

The following studies will be conducted with the optimized GDC-0973 tablet formulation:

1) A Phase 3 study of vemurafenib vs. vemurafenib plus GDC-0973 in previously untreated BRAF<sup>V600</sup> metastatic melanoma patients. All patients are scheduled to have PK sampling to determine exposures of vemurafenib and GDC-0973.

2) A drug-drug interaction study to determine the effect of a CYP3A inhibitor (such as ketoconazole) on GDC-0973 in healthy subjects. The control period will dose GDC-0973 single agent and provide PK data on the optimized tablet.

3) Other clinical pharmacology studies, as needed to support the NDA filing.

The sponsor would like to leverage the information from the following clinical studies:

1) Phase 1 dose escalation study of GDC-0973 in cancer patients where the first three cohorts were dosed with PiB (API in bottle administered as a solution). GDC-0973 C<sub>max</sub> and AUC following solution administration were similar to those observed following PiC (API in capsule) administration at a comparable dose.

2) A clinical pharmacology study to determine the relative BA and food effect study using the PiC and the prototype tablet in healthy subjects. The results from the relative BA study comparing the prototype tablet to PiC showed that both C<sub>max</sub> and AUC met the bioequivalence criteria with 90% CI within 0.8-1.25. Dosing the prototype tablets in the fed vs. fasted state showed comparable exposures.

3) A clinical pharmacology study to see the effect of proton-pump inhibitor (PPI) on GDC-0973 PK using the prototype tablets. GDC-0973 exposures when administered with PPI showed comparable exposures to GDC-0973 administered alone.

4) The Phase 1b combination study of GDC-0973 (PiC formulation) and vemurafenib. Data from this study will be used for PK comparison of the PiC (Phase 1b) and optimized tablet (Phase 3) in melanoma patients.

The Agency stated that the information provided by Genentech/Roche in the meeting package and subsequent communication (see section 5.0) appears to be acceptable. Genentech committed to provide any additional relevant data at Agency's request.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There are no specific issues requiring further discussion at this time.

### **4.0 ACTION ITEMS**

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

### **5.0 ATTACHMENTS AND HANDOUTS**

Handout provided by Genentech/Roche on November 19, 2012, see attached.

### **6.0 CONCURRENCE**

*{See appended electronic signature page}*

Jewell D. Martin, MA, MBA, PMP  
Regulatory Project Manager for Product Quality  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

*{See appended electronic signature page}*

Nallaperumal Chidambaram, Ph.D.  
Acting Branch Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Attachment:  
Genentech/Roche handout provided November 19, 2012.

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JEWELL D MARTIN  
11/28/2012

NALLAPERUM CHIDAMBARAM  
11/28/2012



End-of-Phase 1/Pre Phase 3 109307

## MEETING MINUTES

Hoffman-La Roche, Inc.  
Attention: Matthew Klimek, PharmD  
Senior Program Manager, Drug Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Klimek:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vemurafenib & GDC-0973.

We also refer to the meeting between representatives of your firm and the FDA on June 27, 2012. The purpose of the meeting was to discuss the proposed development plan to support the use of vemurafenib in combination with GDC-0973 for the treatment of patients with unresectable or metastatic melanoma with BRAF<sup>V600</sup> mutations.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager at (301) 796-1273.

Sincerely,

*{See appended electronic signature page}*

Melanie Pierce  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End-of-Phase 1/Pre-Phase 3  
**Meeting Date and Time:** June 27, 2012; 11:30 a.m.-12:30 p.m.  
**Meeting Location:** Bldg. 22 WO conference room 1417  
**Application Number:** 109307  
**Product Name:** Vemurafenib and GDC-0973  
**Indication:** Treatment of patients with unresectable or metastatic melanoma with BRAF<sup>V600</sup>  
**Sponsor/Applicant Name:** Hoffman-La Roche, Inc.  
**Meeting Chair:** Patricia Keegan  
**Meeting Recorder:** Melanie Pierce

**FDA ATTENDEES**

**Office of Hematology and Oncology Products**

Anthony Murgo Associate Director of Regulatory Science

**Office of Hematology and Oncology Products**

**Division of Oncology Products 2**

Patricia Keegan Division Director  
Joseph Gootenberg Deputy Division Director  
Marc Theoret Clinical Reviewer  
Melanie Pierce Regulatory Project Manager

**Office of Hematology Oncology Products**

**Division of Hematology Oncology Toxicology**

Whitney Helms Pharmacology / Toxicology Supervisor  
M.A. Goheer Pharmacology / Toxicology Reviewer  
George Chang Pharmacology / Toxicology Reviewer

**Office of Clinical Pharmacology**

**Division of Clinical Pharmacology V**

Jian Wang Clinical Pharmacology Reviewer

**Office of Biostatistics**  
**Division of Biometrics 5**

Kun He

Biostatistics Team Leader

**SPONSOR ATTENDEES**

Flavia Borellini, PhD  
Gordon Bray, MD

Lifecycle Team Leader  
Global Development Team Leader  
(Vemurafenib)

Nicholas Choong, MD  
Iris Chan, MD, PhD

Clinical Scientist  
Global Development Team Leader (GDC-0973)

Eric Harstad, PhD, DA  
Matthew Klimek, PharmD  
Jennifer Low, MD

Non-Clinical Safety  
US Regulatory Partner  
Clinical Franchise Head, Signaling and Melanoma

Luna Musib, PhD  
Betty Nelson  
Kathleen Winson  
Nathan Winslow

Clinical Pharmacologist  
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## BACKGROUND

On March 21, 2012, Hoffman-La Roche, Inc., submitted a meeting request to discuss the major efficacy trial intended to support [REDACTED]<sup>(b) (4)</sup> vemurafenib, in combination with GDC-0973, and to support an original NDA for GDC-0973 for the treatment of patients with unresectable or metastatic melanoma with BRAF<sup>V600</sup> mutation [REDACTED]<sup>(b) (4)</sup>

[REDACTED] Roche submitted a meeting package on May 25, 2012, that contained the draft protocol GO28141 titled “A Phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma.”

Vemurafenib is a BRAF inhibitor that blocks the function of the V600E-mutated BRAF protein and is currently FDA-approved as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF<sup>V600E</sup> mutation as detected by an FDA approved test.

GDC-0973 is an investigational MEK inhibitor that Roche states has shown anti-tumor activity in multiple xenograft models that harbor mutations for BRAF or KRAS and inhibits the phosphorylation of ERK1/2 and also inhibits proliferation in a panel of cell lines harboring either wild-type or mutant KRAS and/or BRAF.

### **Clinical Trials:**

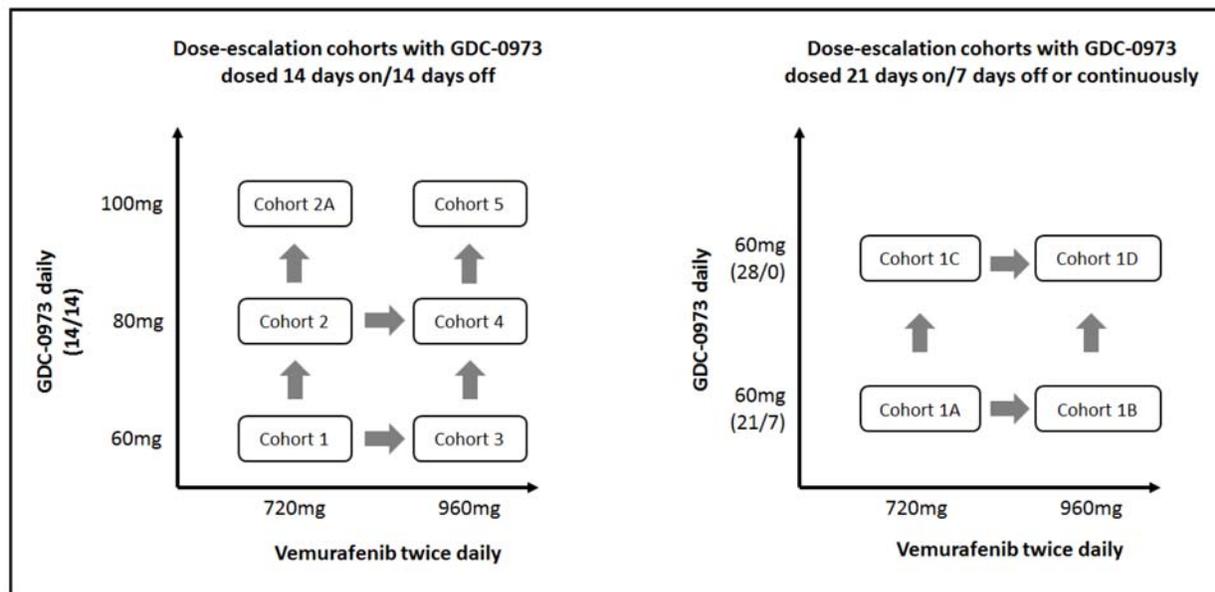
Roche submitted preliminary information from one ongoing clinical trial evaluating of vemurafenib in combination with GDC-0973. Study NO25395 is a Phase 1B, dose-escalation study designed to assess the safety, tolerability, and pharmacokinetics of combination treatment with vemurafenib and GDC-0973. The primary objectives of the trial are:

- To evaluate the safety and tolerability of the vemurafenib and GDC-0973 combination
- To identify the dose limiting toxicities (DLTs) that determine the maximal tolerated dose (MTD) of the vemurafenib and GDC-0973 combination
- To identify a recommended Phase II/III dose and schedule for the vemurafenib and GDC-0973 combination
- To characterize Day 1 and steady-state pharmacokinetics of GDC-0973 when administered in combination with vemurafenib and to characterize the steady-state pharmacokinetics of vemurafenib administered alone and in combination with GDC0973

This study is being conducted in patients, age  $\geq 18$  years with BRAF<sup>V600E</sup> mutation-positive, unresectable locally advanced or metastatic melanoma, who are either vemurafenib naïve or have progressed on vemurafenib treatment. Key inclusion criteria include the presence of V600E mutation in melanoma tumor tissue using the cobas BRAF<sup>V600</sup> mutation test, measurable disease per RECIST v1.1, Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 1$ , and adequate hematologic and end organ function assessed through key laboratory measures.

This open-label, multicenter study has two stages, a dose-escalation stage and a cohort-expansion stage. All patients in the dose-escalation stage receive continuous, twice daily oral vemurafenib in combination with oral GDC-0973 administered once daily by one of the following schedules: 14 consecutive days followed by a 14-day drug holiday (14/14), 21 consecutive days followed by a 7 day drug holiday (21/7), or as a continuous daily dose (28/0). Each treatment cycle is 28 days.

The protocol specifies 10 dose-escalation cohorts of 3–6 patients per cohort (see Figure below).



Patients enrolled in the initial cohort, Cohort 1, received vemurafenib at a dose of 720mg twice daily continuously and GDC-0973 60mg once daily for 14 consecutive days of each 28-day cycle of combination dosing (14/14). After a cohort is declared safe and tolerable, cohort-expansion may be instituted for that specific cohort.

As of March 1, 2012, a total of 37 patients have received combination treatment with vemurafenib and GDC-0973. The most common treatment-emergent adverse events (AEs) observed in Study NO25395 include diarrhea (49%), rash (46%), nausea (35%), fatigue (27%) and photosensitivity (22%). Two patients (5.4%) experienced Grade 3 diarrhea and three patients (8.1%) experienced Grade 3 rash. Two Grade 4 AEs occurred: creatine phosphokinase elevation and tonsil cancer (described in Section 4.1.2.4.5 of the meeting package). Roche reports that there were no Grade 5 events encountered on this study. Of the six patients accrued to the cohort (Cohort 1B) which received vemurafenib and GDC-0973 at the dose and schedule proposed for the registration trial (Trial GO28141), one patient encountered a DLT (Grade 3 QTc prolongation). Roche is currently expanding accrual to Cohort 1B to collect additional safety and pharmacokinetic data.

Roche reports that of the 37 treated patients, 28 were evaluable for efficacy as of the March 1, 2012, data cutoff date. There were four partial responses (PRs) observed during the trial: two confirmed PRs out of the 24 patients who previously progressed on vemurafenib therapy and two

confirmed PRs out of the four patients who were naive to prior treatment with BRAF or MEK inhibitor therapy at study entry.

**Proposed Pivotal Study:**

Study GO28141 is a multicenter, randomized (1:1), double-blind, placebo-controlled clinical trial of vemurafenib in combination with GDC-0973, compared with vemurafenib plus placebo, in 390 patients with previously untreated BRAF<sup>V600E</sup>-mutation-positive, unresectable locally advanced or metastatic melanoma. The primary objective of the trial is to compare the efficacy of vemurafenib in combination with GDC-0973, versus vemurafenib plus placebo, as measured by prolongation of PFS, as assessed by the study investigator. Secondary objectives are:

- To compare the objective response rate, duration of response, and overall survival of patients receiving vemurafenib plus GDC-0973 vs. vemurafenib plus placebo
- To compare the adverse event profile in patients receiving vemurafenib plus GDC-0973 vs. vemurafenib plus placebo
- To examine health-related quality of life of patients receiving vemurafenib plus GDC-0973 vs. vemurafenib plus placebo
- To characterize the pharmacokinetics of GDC-0973 plus vemurafenib and to compare the pharmacokinetics of vemurafenib when administered with GDC-0973 to its pharmacokinetics when administered with placebo

Key eligibility criteria include patients age  $\geq 18$  years with histologically confirmed melanoma, either unresectable Stage IIIC or Stage IV metastatic melanoma; previously naive to treatment; BRAF<sup>V600</sup>-mutation-positive using the cobas BRAF<sup>V600</sup> mutation test; measurable disease by RECIST v1.1; ECOG performance status of  $\leq 1$ ; and no prior treatment with a RAF or MEK inhibitor.

All eligible patients will be randomized to Arm A (vemurafenib plus placebo) or Arm B (vemurafenib plus GDC-0973) using a stratified, permuted-block randomization scheme based on geographic region (North America; Europe; Australia/New Zealand) and metastatic classification (unresectable Stage IIIC, M1A and M1B; or M1C). Randomized patients will receive placebo (Arm A) or GDC-0973 60 mg (Arm B) administered orally once daily on days 1 to 21 of each 28 day cycle. Patients on both arms will receive vemurafenib 960 mg orally twice daily on day 1 to 28 of each 28 day treatment cycle. Study treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest. Patients randomized to Arm A are not permitted to crossover to receive vemurafenib plus GDC-0973 at disease progression.

Tumor response and progression will be evaluated according to RECIST v1.1. Response will be assessed by the investigator at 8 week intervals. Objective response must be confirmed by repeat assessments  $\geq 4$  weeks after initial documentation. In the case of stable disease (SD), tumor measurements must have met the SD criteria at least once after study entry at a minimum interval of not fewer than 6 weeks.

This study will enroll 390 patients from approximately 125 clinical trial sites in North

America, Europe, Australia/New Zealand and other selected countries (to be determined) over a period of approximately 13 months. The study will end when all patients enrolled have been followed until death, withdrawal of consent, or lost to follow up.

The primary endpoint is PFS as assessed by investigator. Assuming that the median PFS is 6 months in the control arm and 11 months in the experimental arm, a total of 167 events are needed to detect a hazard ratio of 0.55 with 95% power at a 2-sided alpha level of 5%. The primary analysis will be a stratified log-rank test performed on the ITT population. The hazard ratio (HR) for PFS will be estimated using a stratified Cox model. Two-sided 95% confidence intervals (CIs) for the hazard ratio (HR) will be provided.

No interim analyses of PFS will be performed.

The trial is also designed to test overall survival (OS). Similar analyses as planned for PFS analyses above will be performed for OS. Assuming that the median OS is 15 months in the control arm and is 20 months in the experimental arm, a total of 296 events are needed to detect a hazard ratio of 0.75 with 62% power at a 1-sided alpha level of 2.5%. Two OS interim analyses will be performed, one after 95 (32%) events corresponding to the final PFS analysis and another after 198 (67%) events. The Pocock boundary method is utilized with alpha allocation of 0.022 for each OS analysis.

Major secondary endpoints include OS and ORR (including duration of ORR). A hierarchical procedure is not proposed to adjust for multiplicity in testing the secondary endpoints.

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## **Sponsor Submitted Questions and FDA Response:**

### **CLINICAL:**

1. Does FDA agree that the scientific rationale and clinical data available to date support initiation of a Phase III registration trial of vemurafenib in combination with GDC-0973 in patients with unresectable or metastatic melanoma with BRAFV600E mutation?

**FDA Response:** The scientific rationale and clinical data appear acceptable to support initiation of a Phase 3 registration trial. However, the meeting package provides limited information concerning the optimal GDC-0973 dose or schedule to evaluate in the proposed registration trial.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

2. With respect to the study design, does FDA agree:
  - a. The randomized, double-blinded, placebo-controlled design(Vemurafenib/GDC-0973 vs. Vemurafenib/Placebo) is acceptable, including the use of investigator assessment for the primary endpoint (PFS).

**FDA Response:** The randomized, double-blinded, placebo-controlled design is acceptable. However, in addition to the investigator assessments of PFS as proposed for analysis of the primary endpoint, assessments of PFS should be subjected to a blinded, independent review committee. Please refer to FDA guidance “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf>.

FDA notes that a blinded independent review for the conduct of clinical trials using investigator-assessed PFS as the primary endpoint will be the subject of an ODAC meeting scheduled for July 24, 2012. Please refer to the Federal Register notice which can be accessed at <https://www.federalregister.gov/articles/2012/05/31/2012-13156/oncologic-drugs-advisory-committee-notice-of-meeting>.

Please also refer to additional FDA comments 4(a) and # 9.

**Roche Response emailed June 27, 2012:** We will archive all scans so that a blinded independent review may be conducted to support the NDA submission. Roche would like clarification from FDA of whether an independent review of a percentage of scans would be adequate as opposed to an independent review of all scans.

**Discussion during the meeting:** FDA stated that comments on an audit of a subset of PFS scans will be deferred pending the upcoming July 24, 2012 Oncology Drugs Advisory Committee discussion on this topic

- b. The proposed target patient population is adequately defined per the study eligibility criteria?

**FDA Response:** Yes, the proposed target patient population appears adequate as defined.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

- c. The selected dose and dosing regimen is appropriate for the proposed indication?

**FDA Response:** FDA is unable to determine if the selected dose and dosing regimen is appropriate based on the data provided in the meeting package.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

- d. The safety monitoring and risk management measures proposed are acceptable?

**FDA Response:** The safety monitoring and risk management measures as proposed should be modified to include the following additional assessments:

- periodic ophthalmic examinations while patients are on-treatment and at the end-of-study to mitigate the risk of a patient developing clinically important central serous retinopathy and retinal vein occlusion
- evaluations for cardiac toxicity, e.g., addition of testing of LVEF (i.e., Echo or MUGA) at baseline and periodically while on treatment
- thorough head and neck examinations

**Roche Response emailed June 27, 2012:** Roche is currently conducting ophthalmic examinations at baseline in all study patients and will exclude from participation patients with findings of or risk factors for either central serous retinopathy (CSR) and/or retinal vein occlusion (RVO). In the current study NO25395 patients undergo follow-up ophthalmic examinations upon presentation of symptoms with visual disturbance. We regard clinically important CSR as those cases with symptoms. RVO is unlikely to be asymptomatic; routine ophthalmologic examinations would not mitigate the risk of a patient developing RVO. Overall, for CSR and RVO in the absence of visual symptoms, we do not believe routine ophthalmic examinations are warranted. Roche would like to better understand the rationale for FDA's request for routine monitoring.

Roche agrees and will conduct evaluations for reduction in LVEF at baseline and periodically while on treatment.

Thorough head and neck examinations are currently planned for patients in study G028141 by the treating physician at baseline for all patients enrolled and at 3-month intervals for all patients thereafter.

**Discussion during the meeting:** FDA requested that additional summary data be provided to support the reversibility of all cases of CSR and show that periodic monitoring would be unlikely to mitigate risks. Roche agreed to provide the data with the final protocol, G028141. In addition, Roche will develop more detailed case report forms to systematically collect information on ophthalmologic CSR and RVO events to include the findings, bases for recommendations, on dosing, dose modification and long term outcomes. Periodic monitoring of asymptomatic RVO events may be warranted.

FDA agreed that this proposed approach to safety monitoring and the approach outlined in the second and third bullets are acceptable.

3. Does FDA agree that the primary efficacy endpoint and secondary endpoints are adequate to evaluate the efficacy of vemurafenib in combination with GDC-0973 in the metastatic melanoma setting?

**FDA Response:** No. Please see FDA comments # 2(a), 4(a), and 5(b). In addition, the adequacy of the planned analyses of the primary and secondary endpoints to support

marketing approval will be determined upon FDA review of the submitted protocol and statistical analysis plan (SAP).

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

4. **Indication:**

- a. Does the FDA agree that one single positive pivotal study, as proposed, would support registration of GDC-0973 for the following indication?

Proposed Indication for GDC-0973:

*GDC-0973 in combination with vemurafenib is indicated for the treatment of patients with (b) (4) unresectable or metastatic melanoma with BRAFV600E mutation (b) (4).*

**FDA Response:** No. Please see FDA responses to Questions # 2(a) and 5(b).

Please note that an NDA based primarily on the results of study GO28141 would require demonstration of a robust effect on PFS that is of sufficient magnitude to be direct evidence of clinical benefit and permit a positive risk-benefit determination—a determination that may also consider the treatment landscape for the proposed patient population at the time of a marketing application as described in 21 CFR 312.84.

Please also note that for a single randomized trial to support an NDA, the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. Please refer to FDA guidances “Providing Clinical Evidence of Effectiveness for Human Drug and Biological products” at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf>

and “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf>.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

- b.

(b) (4)

**FDA Response:** Please see FDA response to Question # 4(a). The specific indication would be discussed during the review of the application.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

5. Statistical Analysis Plan:

- a. Does FDA agree with the proposed plan for the primary analysis of PFS, and in particular with the timing of the analysis, number of PFS events and type one error control?

**FDA Response:** Yes, the proposed primary analysis of PFS is acceptable.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

- b. Does the FDA agree with the planned OS interim and final analyses, in particular with the timing of the analyses, the number of events, and power?

**FDA Response:** No. The final OS analysis should be sufficiently powered to detect clinically important effects on survival, i.e., the required number of deaths for the OS analysis should be increased. For the interim OS analyses, the O'Brien-Fleming boundary method should be used.

**Roche Response emailed June 27, 2012:** We agree to use the O'Brien-Fleming boundary method for the OS analyses.

Roche would like to better understand the FDA request for an increased number of deaths at the final OS analysis. At the time of the current final OS analysis 296 of 390 patients will have died.

The data supporting a NDA submission will be the primary PFS endpoint; final OS analysis will not be available at the time of NDA submission. Roche would like to clarify if a positive primary endpoint of PFS will be sufficient to support a NDA submission for the proposed indication?

**Discussion during the meeting:** FDA clarified that an NDA submission based on the primary endpoint of PFS, which meets the criteria outline in our response to 2a and 4a would be sufficient to support an NDA submission. However, FDA still requests that the trial be adequately powered (80%) to detect a clinically

important effect on OS. This may be achieved by increasing the sample size as well as the number of death events at the time of final analyses. FDA will evaluate the interim OS data at the time of the NDA submission both for supportive evidence of efficacy and for assessment of safety.

6. Does the FDA agree that the proposed safety database with approximately 245 vemurafenib/GDC-0973-treated patients is sufficient to characterize the safety profile of this combination in this patient population?

**FDA Response:** It would be premature to determine the adequacy of the proposed safety database to characterize the safety profile of vemurafenib in combination with GDC-0973 in this patient population based on the limited information from trial NO25395 regarding patients treated at the proposed dose and schedule of the combination.

In support of the proposed protocol, please provide up-to-date safety information from trial NO25395 as well as all planned safety assessments in the registration trial in the IND amendment that contains the Study GO28141 protocol.

Please also see the FDA response to Question # 2(d).

**Roche Response emailed June 27, 2012:** Roche will provide FDA with up-to-date safety information from trial NO25395 at the time of the IND amendment for Study GO28141. All planned safety assessments will be included in the final protocol.

**Discussion during the meeting:** There was no further discussion during the meeting.

#### **CLINICAL PHARMACOLOGY:**

7. Does FDA agree that the planned clinical pharmacology program is sufficient to support registration for the proposed indication?

**FDA Response:** No. In addition to the proposed clinical pharmacology program provided to the meeting package, the sponsor should include the following in the NDA submission:

- A drug interaction study evaluating the effect of strong CYP3A4 inducers (e.g. rifampin) on GDC-0973 pharmacokinetics
- Dedicated Hepatic and renal impairment trials for GDC-0973 or justification for not conducting such studies based on the results from the planned mass balance study.

**Roche Response emailed June 27, 2012:** We will be conducting a drug interaction study evaluating effect of a strong CYP3A inhibitor (eg. Ketoconazole or Itraconazole) on GDC-0973 pharmacokinetics. We intend to gate the decision on whether or not to conduct a study with a strong CYP3A inducer based on the results of the CYP3A inhibitor study.

We agree with the approach to gate the dedicated hepatic and renal impairment trials on the results from the human mass balance study. We plan to have a future dedicated Type-C meeting to discuss the Clinical Pharmacology program of GDC-0973.

**Discussion during the meeting:** There was no further discussion during the meeting.

- a. Does FDA agree the triplicate ECG monitoring and planned concentration-QTc assessments in the Phase 3 study are sufficient and no dedicated QT study is required to support registration?

**FDA Response:** In principle Roche's approach seems reasonable; however, FDA cannot agree with the proposal at this time. Please submit the QT assessment protocol for FDA review. Furthermore, please provide details regarding the proposed exposure-response analysis.

In order to elucidate the concentration-response relationship for GDC-0973, it is important to collect pharmacokinetics (PK) and ECG's over a period of 24 hours (adequately capturing  $T_{max}$ ) at steady state in order to ensure a wide range of concentrations.

If GDC-0973 (b) (4), a thorough QT (TQT) study may need to be conducted to adequately characterize the QT effect.

**Roche Response emailed June 27, 2012:** The planned QTc assessments are incorporated in the respective protocols for Phase Ib study NO25395 and Phase III study GO28141. A separate QT assessment protocol is not planned. We will provide details regarding the proposed exposure-response analysis, including concentration-QTc analysis, at a future Type-C meeting to discuss the Clinical Pharmacology Program in detail. Does FDA agree a separate QT assessment protocol is not necessary?

Roche anticipates submitting exposure QTc response data for GDC-0973 from the following studies where both day 1 and steady state concentration QTc data will be available:

- MEK4592g Phase 1a (GDC-0973 monotherapy), n=97.
- NO25395 Phase 1b (GDC-0973/Vemurafenib), n= approximately 100.
- GO28141 Phase 3 (GDC-0973/Vemurafenib), n=approximately 200

Does FDA agree that this dataset will be sufficient to adequately define the exposure QTc response for the NDA submission?

**Discussion during the meeting:** FDA will follow-up with the Interdisciplinary Review Team (QT-IRT) to address Roche's response.

**FDA Post-meeting response:** FDA agrees that the proposed dataset will be sufficient to adequately define the exposure QTc response. Please refer to comment 11 concerning time points for ECG collection.

- b. Does FDA agree with the proposed plan to evaluate the pharmacokinetics of vemurafenib and GDC-0973 in the Phase 3 study

**FDA Response:** The proposed plan to evaluate the pharmacokinetics of vemurafenib and GDC-0973 in Study GO28141 appears acceptable.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

- c. Does FDA agree a dedicated drug-drug interaction study of vemurafenib in combination with GDC-0973 is not needed to support registration?

**FDA Response:** The need to conduct a dedicated drug-drug interaction study of vemurafenib in combination with GDC-0973 will be determined upon review of the DDI results from the ongoing trial, NO25395, and the proposed trial, GO28141.

**Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.

**Discussion during the meeting:** There was no further discussion during the meeting.

#### NONCLINICAL:

8. Does FDA agree that the proposed non-clinical program is sufficient to support registration for the proposed indication?

**FDA Response:** The studies described in the meeting package are not sufficient to support the filing of an NDA for the proposed combination. In addition to the studies described in the meeting package, a reproductive assessment (embryofetal toxicology studies) and an *in vivo* genotoxicity study of GDC-0973 are also required to support NDA filing. The potential for GDC-0973-mediated phototoxicity should also be addressed in the submission. For further details, please see Guidance for Industry, ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals.

([http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085389.pdf?utm\\_campaign=Google2&utm\\_source=fdaSearch&utm\\_medium=website&utm\\_term=ich\\_s9&utm\\_content=1](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085389.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=ich_s9&utm_content=1)).

**Roche Response emailed June 27, 2012:** Roche agrees and will conduct the requested studies.

**Discussion during the meeting:** FDA clarified that if a rat embryofetal toxicity study is positive for teratogenic effects, a rabbit study would not be required. If a dose-range finding study in pregnant rats is sufficiently designed, a definitive study may not be warranted. Roche proposed inclusion of a standard *in vitro* phototoxicity assay to address phototoxicity. FDA found this proposal acceptable.

**ADDITIONAL FDA COMMENTS:**

9. Regarding the proposed design and conduct of trial GO28141:
- a. In order to minimize “informative censoring,” missing data should be kept to a minimum in order to consider PFS results to be robust, verifiable, and free from potential bias. Patients discontinuing treatment for symptomatic deterioration (or for any other reason) without objective documentation of disease progression should continue to be followed to avoid a high proportion of censoring due to loss of follow-up.
- Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.
- Discussion during the meeting:** There was no further discussion during the meeting.
- b. The case report forms (CRF) should capture detailed information about non-target lesions at baseline, including the site of the lesion(s), as well as qualitative information concerning the response of each lesion at each tumor assessment time point.
- Roche Response emailed June 27, 2012:** Roche thanks FDA for their response and has no further comments.
- Discussion during the meeting:** There was no further discussion during the meeting.
10. FDA requests that Roche provide follow-up for second primary malignancies from the proposed trial annually and one year after the last patient has completed clinical trial treatment.
- Roche Response emailed June 27, 2012:** Roche agrees and will modify the protocol as requested.
- Discussion during the meeting:** There was no further discussion during the meeting.
11. FDA recommends ECG monitoring for all patients in all on-going and future clinical trials. The suggested time points include baseline,  $T_{max}$  for the parent compound and major metabolites for vemurafenib and GDC-0973, at the first dose and at steady state, and periodically during the treatment.

**Roche Response emailed June 27, 2012:** Roche intends to conduct ECG monitoring for all patients in accordance with the vemurafenib USPI. Vemurafenib has minimal fluctuation (Cmax to Cmin ratio of ~1). Additionally, GDC-0973 shows no evidence of QT prolongation from the GDC-0973 monotherapy Phase Ia trial at doses up to 125 mg (more than 2-fold greater than the proposed Phase 3 dose). Therefore, Roche believes that the evaluation pre-dose on D15 (steady-state) of Cycle 1, 2 and 3 is sufficient.

Roche would like to discuss the Tmax time point recommendation further at the meeting.

**Discussion during the meeting:** FDA's recommendation for ECG monitoring is for safety purposes. Roche's proposed ECG monitoring plan appears acceptable provided there are no cardiac safety signals. The QT-IRT team will provide additional advice at a later time.

**FDA Post-meeting response:** QT-IRT concluded that GDC-0973 has the potential to prolong QTc. Because of the limited clinical safety database available so far, it is hard to exclude QT liability associated with GDC-0973. Therefore, ECG monitoring should be performed at timepoints that include the GDC-0973 Tmax.

#### **ISSUES REQUIRING FURTHER DISCUSSION**

- See action items below

#### **ACTION ITEMS**

- FDA agrees to provide written responses to items 7a and 11 with a follow-up teleconference if needed.

#### **ATTACHMENTS AND HANDOUTS**

- There are no attachments or handouts



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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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MELANIE B PIERCE  
07/26/2012

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 206192

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Genentech, Inc.  
Attention: Sarah Wayson, Ph.D.  
Regulatory Program Management  
One DNA Way, MS 241A  
South San Francisco, CA 94080-4990

Dear Dr. Wayson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Cotellic [Proposed] (Cobimetinib).”

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 20, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call me at (301) 796-1721.

Sincerely,

*{See appended electronic signature page}*

Meredith Libeg  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** Wednesday, May 20, 2015; 1:00 PM – 2:00 PM (ET)

**Meeting Location:** 10903 New Hampshire Avenue (Teleconference)

**Application Number:** NDA 206192

**Product Name:** Proposed name: Cotellic (cobimetinib)

**Indication (Proposed):** For the use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation

**Sponsor/Applicant Name:** Genentech, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

**BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE**

1. Discipline Review Letters

- No Discipline Review letters have been issued to date.

2. Substantive Review Issues

- The following substantive review issues have been identified to date:
  - Discussion on data integrity issues and potential impact on the interpretation of the safety information in the submission of the original NDA
  - Discussion on ocular toxicity
  - Discussion on abuse potential
  - Labeling –BRAF V600 mutation subtype

**ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

**LCM AGENDA**

1. Introductory Comments – 5 minutes (RPM/CDTL)
  - Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 10 minutes
  - Each issue as noted above will be introduced by FDA and followed by a discussion.
3. Additional Applicant Data – 5 minutes (Applicant)
4. Information Requests – 5 minutes
5. Potential Post-Marketing Commitments/Requirements (PMRs/PMCs) – 10 minutes
6. Major labeling issues – 15 minutes
7. Review Plans – 5 minutes
8. Wrap-up and Action Items – 5 minutes

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/s/  
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MEREDITH LIBEG  
05/20/2015