

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202429Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202429

SUPPL #

HFD # 150

Trade Name Zelboraf

Generic Name vemurafenib

Applicant Name Hoffmann-La Roche Inc.

Approval Date, If Known August 17, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)1

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

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

YES

NO

If yes, explain:

=====

Name of person completing form: Theresa Ferrara, MPH

Title: Regulatory Project Manager

Date: August 16, 2011

Name of Office/Division Director signing form: Robert Justice, MD, MS

Title: Division Director, Division of Drug Oncology Products

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

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

/s/

THERESA A FERRARA
08/16/2011

ALICE KACUBA
08/16/2011

ROBERT L JUSTICE
08/16/2011



DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in cursive script, reading "Judith Siegel", written over a horizontal line.

Judith Siegel, PhD
Vice President, Pharma Development Operations

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202429 BLA #	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Zelboraf Established/Proper Name: vemurafenib Dosage Form: 240 mg Tablets		Applicant: Hoffmann-La Roche, Inc Agent for Applicant (if applicable):
RPM: Theresa Ferrara		Division: DDOP
<p>NDA: 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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 28, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
<p>❖ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1 - NME</p> <p> <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 checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>Comments:</p>	
<p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ 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
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	X
Officer/Employee List	
❖ 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	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval, August 17, 2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	August 11, 2011 - agreed to
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	April 27, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.

❖ 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 checked="" type="checkbox"/> Medication Guide <input 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"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	X
<ul style="list-style-type: none"> Original applicant-proposed labeling 	April 27, 2011
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A
❖ Labels (full color 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"> Most-recent draft labeling 	August 11, 2011 - final C/C
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	Acceptability letter - June 8, 2011 OSE review - June 2, 2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA May 27, 2011 <input checked="" type="checkbox"/> DRISK July 22, 2011 <input checked="" type="checkbox"/> DDMAC July 19, 2011 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM filing review - July 27, 2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>orphan designation</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	X

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg January 21, 2011
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg May 15, 2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	EOP2 CMC mtg July 17, 2009
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 16, 2011
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 16, 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 10, 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 10 (7 PRMs & 3 PMCs)
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	August 1, 2011
• Clinical review(s) (<i>indicate date for each review</i>)	August 1, 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<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>)	See MOR
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None QT/IRT June 2, 2011
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• 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>)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested July 28, 2011

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None August 11, 2011
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 15, 2011
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 15, 2011; Addendum: July 28, 2011
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 18, 2011
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 18, 2011
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 18, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)		<input checked="" type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 28, 2011
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 27, 2011
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 27, 2011
❖ 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
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 19, 2011
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 19, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None July 19, 2011; Supplemental Rev: August 9, 2011
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)		<input type="checkbox"/> None ONDQA Biopharm July 8, 2011

❖ 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 CMC review, July 19, 2011
<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"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: July 19, 2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

THERESA A FERRARA
08/17/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, August 10, 2011 2:08 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: RE: NDA 202429 revisions to carton & container label

Hi Linda,

Please revise the carton and container label to have the revised storage temperature statement (as consistent with the PI and MG), which is listed below:

Store at room temperature 20°C -25°C (68°F -77°F); excursions permitted between 15°C and 30°C (59° F and 86° F).

Thank you.
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Wednesday, August 10, 2011 12:09 PM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: RE: NDA 202429 minor changes to PI & MG - please respond by tomorrow 5pm

Theresa,

Does it make sense to hold the submission of the USPI and MedGuide until we have your response to our question about similar changes in the carton/container label or should we proceed as planned and submit the USPI and MedGuide today? We are ready to take either path.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]

Sent: Wednesday, August 10, 2011 8:43 AM
To: Burdette, Linda {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: RE: NDA 202429 minor changes to PI & MG - please respond by tomorrow 5pm

Hi Linda,
As long as the text in the printed version is in the 2 column format (and the "boxes" are invisible after printing), it will be fine.
Thank you.

I also wanted to let you know that we are experiencing some phone issues at the FDA campus today in case you try to call me.

Take care,
Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Tuesday, August 09, 2011 6:33 PM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: RE: NDA 202429 minor changes to PI & MG - please respond by tomorrow 5pm

Theresa,

Just a quick clarification question on the formatting request.

The "boxes" around the side effects and reportable signs and symptoms are invisible tables in the printed versions and much easier to work with than column format for our printers. As long as the text looks the same (ie, appears in the printed version of the label to be in two column format), can we keep using the invisible table format approach?

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Tuesday, August 09, 2011 5:01 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Kacuba, Alice; Berkhin, Maria {PDR4~Nutley}
Subject: NDA 202429 minor changes to PI & MG - please respond by tomorrow 5pm
Importance: High

Dear Linda,
There are a few minor changes that have been introduced into the PI and Med Guide, referring to the storage of Zelboraf. Additionally, for the Med Guide, please make a formatting change to use the 2 column format for the side

effects and reportable signs and symptoms (rather than the boxes that are currently there). Please review and indicate your acceptance of these changes.

This will constitute our final agreed upon changes (if you have no other comments/edits).

We ask for a response back by tomorrow COB (5pm).

Thank you.

Best regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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THERESA A FERRARA
08/10/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Tuesday, August 09, 2011 5:01 PM
To: Burdette, Linda {PDR4-Nutley}
Cc: Kacuba, Alice; 'Berkhin, Maria'
Subject: NDA 202429 minor changes to PI & MG - please respond by tomorrow 5pm
Importance: High
Attachments: Zelboraf_FDArevised USPI_09AUG2011.doc

Dear Linda,

There are a few minor changes that have been introduced into the PI and Med Guide, referring to the storage of Zelboraf. Additionally, for the Med Guide, please make a formatting change to use the 2 column format for the side effects and reportable signs and symptoms (rather than the boxes that are currently there). Please review and indicate your acceptance of these changes.

This will constitute our final agreed upon changes (if you have no other comments/edits).

We ask for a response back by tomorrow COB (5pm).

Thank you.

Best regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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THERESA A FERRARA
08/09/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Thursday, August 04, 2011 2:42 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib revised PI & MG - response by Aug. 8th
Importance: High
Attachments: NDA202429 PI Roche 8_4_11_FDARevised.doc; FDARevised8-4-11_NDA 202429 vemurafenibMG.doc

Dear Linda,

Please find attached the FDA revised PI and the revised Medication Guide document for NDA 202429 (vemurafenib) Zelboraf. Please review (using track changes for acceptance and/or edits) and merge the Medication Guide document back into the PI and delete the old one (which was in yellow highlight).

We ask for your response by Monday, August 8th COB (by 5pm). Thank you.

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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THERESA A FERRARA
08/04/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, August 03, 2011 2:12 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: RE: NDA 202429 vemurafenib CMC IR - ADDITIONAL COMMENT
Importance: High

Dear Linda,

Thank you for the recent submission. The CMC review team has one additional comment, listed below. If possible, please respond by tomorrow, 12 noon. Thank you.

To capture the clarification provided in your recent submission, add a list of attributes tested to the post-approval stability programs for Drug Substance and Drug Product (b) (4). The list entitled "The following items will be tested..." which has been recently added to your Drug Product Post-Approval Stability Program section of the NDA will suffice as format. The attributes listed in your recent submission in response to FDA Comment #3 are acceptable.

Sincerely,
Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Wednesday, August 03, 2011 12:04 PM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: FW: NDA 202429 vemurafenib CMC IR - please respond by Wed.Aug 3rd 12noon
Importance: High

Dear Theresa,

Please find attached the CMC response to the information request of August 1, 2011 that has been emailed to Drs. Pope and Goldie. The response will also be formally submitted to NDA 202429 later today.

As an FYI, I will be out of the office this afternoon and on Friday, but am reachable by cell phone (b) (6) and email. In addition, I believe you have Maria Berkhin's contact information (973-235-6742).

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Steinbach, Richard {PT -- Nutley}

Sent: Wednesday, August 03, 2011 11:43 AM
To: sarah.pope@fda.hhs.gov; scott.goldie@fda.hhs.gov
Cc: Burdette, Linda {PDR4~Nutley}; Voss, Duane {PT --Nutley}
Subject: FW: NDA 202429 vemurafenib CMC IR - please respond by Wed.Aug 3rd 12noon
Importance: High

Dear Drs. Pope and Goldie,

Please find attached the requested information to address the four (4) comments listed in the below August 1, 2011 e-mail to Dr. Burdette. The requested quality information and data is provided in follow-up to previous correspondence supplied in Information Amendment S0032 dated July 29, 2011 for the Vemurafenib 240 mg (b) (4) validation batches manufactured in accord with NDA 202429.

Our responses are being sent by email and we are also submitting the response through the gateway today as well.

In Duane Voss's absence, please feel free to contact me directly.

Thanks and kindest regards,

Rich

Richard J. Steinbach B.S. Pharm. R.Ph.

Hoffmann-La Roche Inc.

Group Director - Pharma Technical Regulatory

340 Kingsland Street

Nutley, New Jersey USA Bldg 1/ fl.2A20

Tele: # 973-235-7006

Fax: # 973-562-3700

"I urge all of you to enjoy your life, the precious moments you have. To spend each day with some laughter and some thought, to get your emotions going. To be enthusiastic every day." the late Jim Valvano

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Monday, August 01, 2011 4:04 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib CMC IR - please respond by Wed.Aug 3rd 12noon
Importance: High

Hi Linda,

Please refer to NDA 202429 (vemurafenib) and the launch batch amendment received July 29, 2011.

Please respond to the CMC comments listed below by Wednesday, August 3rd, 12noon. Thank you. Let me know if there are any questions or concerns.

1. Provide a revised version of Table 9 "Results from release testing of (b) (4) (b) (4) to include chemical and physical data for all 15 batches used in the manufacture of the drug product validation batches (M0020, M0021 and M0022). The submitted version includes

only chemical data, no physical data (i.e. psd, density and crystallinity) for only five batches (BS10120011-15). Further, the tabulated data in the rows under each single batch heading column appears to belong to several batches. Verify and correct the data in the table.

2. For Tables 10, 11 and 12 - provide physical data (i.e. psd, density and crystallinity) from the 3 months stability testing of the three (b) (4) batches (BS10120011-13) used in the manufacture of the drug product validation batches. Only chemical data was provided.

3. Confirm that the following attributes listed below are to be included in your post-approval stability program for drug substance, drug product intermediate and drug product:

a. Drug Substance:

Chemical: Assay, Related substances (b) (4), RO6800730, RO6800725, (b) (4), Unspecified each, Total of all)

Physical: Appearance, Color, Water Content, Identity, Modification by XRPD.

b. Drug Product (b) (4)

Chemical: Assay, purity, Related substances ((b) (4), RO6800730, RO6800725, (b) (4), RO6800726, (b) (4), Unspecified each, Total of unspecified max, Total of all)

Physical: Appearance, Color, Water Content, Identity, Particle Size Distribution (b) (4), Bulk Density, Modification by XRPD.

c. Drug Product (film-coated tablets):

Chemical: Content of RO5185426-000, % of claim, Unspecified Degradation Products, Total of all,

Physical: Description (Color), (b) (4) and dissolution.

4. Revise the Drug Product Stability Commitment in Section 11, Table 15 to include the proposed (b) (4)

Best regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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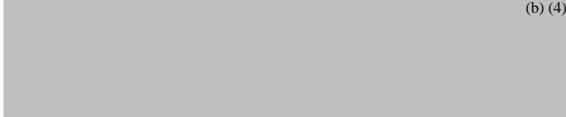
THERESA A FERRARA
08/03/2011

Ferrara, Theresa

From: Fourie Zirkelbach, Jeanne
Sent: Thursday, July 28, 2011 12:51 PM
To: 'Burdette, Linda'
Cc: Ferrara, Theresa; Liu, Qi (CDER)
Subject: Vemurafenib NDA urgent information request for Clinical Pharmacology Reviewer.

Importance: High

Hi Linda,
Could you please notify us which of your clinical trials had clinical pharmacokinetic samples collected at the following site:



We kindly request an immediate response to this information request.

Thanks for your help.
Regards,
Jeanne

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THERESA A FERRARA
07/28/2011

MEMORANDUM OF TELECON

DATE: July 28, 2011

APPLICATION NUMBER: NDA 202429

BETWEEN:

Name: Linda Burdette
Phone: (b) (4) passcode (b) (4)
Representing: Hoffman-La Roche, Inc

AND

Name: Theresa Ferrara
Division of Drug Oncology Products

SUBJECT: CMC commercial launch batches

There were prior CMC tele-conference discussions regarding information requests relevant to the review of NDA 202429 – specifically these occurred on Tuesday, June 21, 2011, Monday, June 27, 2011 and Tuesday, July 12, 2011.

The purpose of today's tele-conference is to gain clarification on why the previously-discussed NDA batches, (b) (4) (included in the original NDA submission) are not intended to be used for commercial launch. The following individuals participated on this call:

FDA attendees:

Richard Lostritto, PhD, Director, Division of New Drug Quality Assessment I
Sarah Pope Miksinski, PhD, Chief, Branch 2
Robert Justice, MD, Director, Division of Drug Oncology Products
Amna Ibrahim, MD, Deputy Director, Division of Drug Oncology Products
Alice Kacuba, RN, MSN, RAC, Chief Project Management, Division of Drug Oncology Products
Theresa Ferrara, MPH, Regulatory Project Manager, Division of Drug Oncology Products

Hoffman-La Roche attendees:

Linda Burdette, PhD, Drug Regulatory Affairs
Richard Steinbach, Technical Regulatory Affairs
Simone Weiland, Technical Regulatory Affairs
Larry Cain, PhD, Technical Regulatory Affairs
Catrin Hartleif, Technical Regulatory Affairs
Lauren Merendino, Technical Regulatory Affairs

Discussion: FDA referenced previous discussions/agreements with the Applicant and inquired as

to why the NDA batches would not be used for the commercial launch of vemurafenib. The applicant replied that those batches were made before the validation process. These pre-validation batches were produced at commercial scale, but could not be used for marketing, as they were produced prior to validation. FDA asked the Applicant to confirm this new approach. The Applicant responded and confirmed the new proposal to commercialize batches which were not part of the NDA submission. The Agency stated that this proposal was contrary to previous understanding (reference to teleconference held on 12-JUL-2011). The Applicant then re-confirmed that the batches proposed for launch were not currently part of the NDA submission.

FDA stated that the Applicant would need to submit all supportive data that would link the intended commercial launch batches (M0020, M0021, and M0022) with full CMC information contained the NDA. The Applicant agreed to provide this data.

Additionally, FDA asked for a projected timeline of when this data would be submitted to the NDA as a CMC amendment. The Applicant responded that they would work on gathering all the data needed for this submission. They also replied that they would need to consult their colleagues in Basel, Switzerland and would provide a projected date of submission at a later time.

Furthermore, FDA stated that the action date for this pending application would be delayed by 2-3 weeks as a result of the outstanding CMC issues discussed during this tele-conference.

This tele-conference ended at 4:41pm.

Theresa Ferrara, MPH
Regulatory Project Manager

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/s/

THERESA A FERRARA
08/16/2011



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Chemistry, Manufacturing and Controls Guidance

Meeting Date and Time: Monday, June 27, 2011 1100 – 1200 ET
Meeting Location: Teleconference

Application Number: NDA 202429
Product Name: Vemurafenib (R05185426)
Indication: BRAF^{v600} mutation-positive unresectable or metastatic melanoma
Sponsor/Applicant Name: Hoffman-La Roche Inc.

Meeting Chair: Anne Marie Russell, PhD
Meeting Recorder: Scott N. Goldie, PhD

FDA ATTENDEES

Office of New Drug Quality Assessment

Scott N. Goldie, PhD Chemist/Sr. Regulatory Health Project Manger for Quality
Richard T. Lostritto, PhD Director, Division of New Drug Quality Assessment I (6 July 2011)
Sarah Pope Miksinski, PhD Chief, Branch 2
Anne Marie Russell, PhD Chemistry Reviewer (6 July 2011)

Division of Drug Oncology Products

Amy Tilley Regulatory Project Manager

SPONSOR ATTENDEES

Duane Voss Technical Regulatory Affairs, Nutley
David Ridge PhD Technical Regulatory Affairs, Nutley
Richard Steinbach, B Pharm Technical Regulatory Affairs, Nutley
Rina Gamboni PhD Technical Regulatory Affairs, Basel
Fabian Schwarb PhD Technical Regulatory Affairs, Basel
Walfrido Antuch Garcia PhD Technical Regulatory Affairs, Basel
Anni Pabst Ravot PhD Formulation Development, Basel
Hans-Juergen Mair PhD Chemical Process Development, Basel
Markus Deichmann PhD Quality Assurance, Development, Basel
Catrin Hartleif Quality Assurance, Commercial, Basel
Maria Angela Girometta PhD Technical Regulatory Affairs, Segrate

1.0 BACKGROUND

- 17-Jun-2011: FDA sent information request (IR) #2 to Roche, requested response by 24-Jun and requested a teleconference on 21-Jun to discuss plan to submit requested information.
- 21-Jun-2011: Teleconference to discuss IR#2 – see internal meeting minutes. All issues except #4 resolved on which FDA requested additional information.
- 22-Jun-2011: Roche submitted additional information requested for #4.
- 24-Jun-2011: Roche submitted response to IR#2, FDA requested teleconference on 27-Jun to discuss #4

In the Pre-NDA meeting (Dec 2010), FDA agreed to Roche proposal for

- 1.1 an expiry for the drug product intermediate, (b) (4)
- 1.2 an expiry of the tablet to begin at the time of excipient addition to (b) (4) at the Segrate, Italy tablet site. The basis of the shelf life will be the tablet expiry.

2.0 DISCUSSION



3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion at the conclusion of the meeting.

4.0 ACTION ITEMS

At the conclusion of the teleconference, Roche agreed to submit the agreed upon materials by noon July 5, 2011.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Chemist/Sr. Regulatory Health Project Manager - Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Anne Marie Russell, Ph.D.
Review Chemist, Branch 2
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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/s/

SCOTT N GOLDIE
07/08/2011

ANNE M RUSSELL
07/08/2011

MEMORANDUM OF TELECON

DATE: July 26, 2011

APPLICATION NUMBER: NDA 202429

BETWEEN:

Name: Linda Burdette, Director, Regulatory Affairs
Phone: (b) (4)
Representing: Hoffmann-La Roche, Inc.

AND

Name: Theresa Ferrara
Division of Drug Oncology Products

SUBJECT: Labeling Discussion for NDA 202429 Zelboraf (vemurafenib)

The FDA-revised product label for Zelboraf was conveyed to the applicant on Wednesday, July 20, 2011. However, the applicant stated on July 22, 2011 that the revised label was not received. The label was resent on July 22, 2011.

On July 25, 2011, the applicant requested to have a teleconference with the FDA to discuss specific sections of the FDA revised Zelboraf's label, including Sections 5.10 (BRAFF^{V600E} Testing), 1 (Indications and Usage), and 12.1 (Mechanism of Action). The teleconference was held on July 27, 2011 3:30 pm.

The participants on the Tele-conference are as follows:

From Roche:

Linda Burdette, Regulatory
Nathan Winslow, Regulatory
Chris Bowden, VP Oncology Clinical Development
Richard Lee, Clinical Science Lead
Andrew Joe, Clinical Science
Jake Zeffren, Drug Safety
Peter Compton, Biometrics
Joe Grippo, Clinical Pharmacology
Angelique Braen, Toxicologist
Lauren Merendino, US Business Leader
Flavia Borellini, Team Leader

From Roche Molecular Systems:

Angela Tucker, Regulatory Affairs
Ken Hood, Regulatory Diagnostics
Lesley Farrington, Regulatory Diagnostics
Jeff Lawrence, Medical Affairs

Suzanne Cheng, Research
Brian Earp, International Business Leader
Lara Hashimoto, Diagnostics Team Leader

From Plexxikon:

Keith Nolop, Chief Medical Officer
Gideon Bollag, Nonclinical Pharmacology

From FDA:

Robert Justice, M.D., Division Director, DDOP
Amna Ibrahim, M.D., Deputy Division Director, DDOP
John Johnson, M.D., Clinical Team Leader, DDOP
Max Ning, M.D., Cross Discipline Team Leader, DDOP
Geoffrey Kim, M.D., Clinical Reviewer, DDOP
Amy McKee, M.D., Clinical Reviewer, DDOP
Whitney Helms, Ph.D., Team Leader Pharmacology/Toxicology, DDOP
W. David McGuinn, Ph.D. Pharmacology/Toxicology Reviewer, DDOP
Robeena Aziz, Ph.D., Pharmacology/Toxicology Reviewer, DDOP
Casey Xu, Ph.D., Statistical Reviewer
Donna Roscoe, Ph.D., CDRH
Robert Becker, Ph.D., CDRH
Abraham Tsou, Ph.D., CDRH
Karen Bijwaard, Ph.D., CDRH
Richard Lyght, DDMAC
Theresa Ferrara, MPH, Regulatory Project Manager

Teleconference Discussion:

Following introductions, Hoffmann-La Roche began with Section 5.10 BRAF^{V600E} Testing. The applicant acknowledged that the cobas V600 Mutation Test is designed to test the BRAF V600E mutation, but also stated that the test is able to identify other mutations, including V600K. (b) (4)

[REDACTED]

As a result, the applicant agreed to label the product for patients with metastatic or unresectable melanoma with the BRAF V600E mutation as detected by an FDA approved test.

Roche also agreed to an FDA-proposed addition of Limitation of Use in Section 1. FDA accepted the applicant's modifications of the addition to "Zelboraf is not recommended for use in patients with wild-type BRAF melanoma."

For Section 12.1, (Mechanism of Action), FDA discussed the fact that the drug inhibits both mutated and wild-type forms of BRAF. Having considered the demonstration of Zelboraf's anti-tumor effects in cellular and animal models of melanomas with mutated BRAF^{V600E}, FDA agreed to the

applicant's proposal to list the inhibitory effect of Zelboraf on wild-type BRAF along with other kinases mentioned in Section 12.1.

In addition, Hoffmann-La Roche inquired about projected timelines for completion of labeling and regulatory action on the application. Dr. Justice replied with "soon" and followed it up with probably "Thursday" of this week, with a regulatory action probably early next week assuming all issues are resolved satisfactorily. Dr. Justice also informed them that they would receive a copy of draft [REDACTED] ^{(b)(4)} from Susan Lange in the Office of Oncology Drug Products.

The conference ended approximately at 4:00 pm.

Theresa Ferrara, MPH
Regulatory Project Manager

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/s/

THERESA A FERRARA
08/04/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Tuesday, July 26, 2011 5:50 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 FDA revised PI and MG
Importance: High
Attachments: NDA202429 PI 7 26 11_FDAreviewed.doc; NDA 202429 vemurafenibMG 7_26_11.doc

Dear Linda,
Please find attached the FDA revised PI and MG (dated for today, July 26, 2011) for NDA 202429. Please be sure to use track-changes for any acceptance or edits.

Thank you. We ask for your response back no later than Thursday, July 28th 9am.

Best regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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



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/s/

THERESA A FERRARA
07/26/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Friday, July 22, 2011 6:21 PM
To: 'linda.burdette@roche.com'
Cc: Kacuba, Alice
Subject: NDA 202429 Zelboraf - PI section 14

Dear Linda,

It was recently brought to my attention that there was one modification to the PI in section 14 under Clinical Studies – the addition of the words “**investigator-assessed**” in the 2nd to last sentence of the paragraph. It is high lighted below in yellow. This was not captured in the PI version that was recently sent to you.

Also, I wanted to point out about the Medication Guide – it should not be labeled as section 17.2. Rather, it will begin on the next page (so will need to put in a page break.)

Please call me if you have any questions or concerns.

Have a good weekend.

Theresa

14 CLINICAL STUDIES

Treatment-Naive Patients

The efficacy and safety of Zelboraf in patients with treatment-naïve, BRAF^{V600E} mutation-positive unresectable or metastatic melanoma were assessed in an international, randomized, open-label trial (Trial 1). The trial enrolled 675 patients; 337 were allocated to receive vemurafenib 960 mg by mouth twice daily and 338 to receive dacarbazine 1000 mg/m² intravenously on Day 1 every 3 weeks. Randomization was stratified according to disease stage, lactate dehydrogenase (LDH), ECOG performance status and geographic region. Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. The major efficacy outcome measures of the trial were overall survival (OS) and investigator-assessed progression-free survival (PFS). Other outcome measures included confirmed investigator-assessed best overall response rate

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
07/22/2011

Ferrara, Theresa

From: El Hage, Antoine N
Sent: Friday, July 22, 2011 1:45 PM
To: Ferrara, Theresa; Ning, Yang-Min (Max)
Cc: Young, Robert S K; Iacono-Connor, Lauren; Mulinde, Jean
Subject: FW: Urgent - NDA 202429 Status of Inspections Request

Hi Theresa,

On behalf of Dr Young, I am providing you with an update on the status of the 4 inspections and a sponsor inspection:

1. Sponsor inspection at Roche just last week (7/8) with an NAI classification. All monitoring activities are completed by their contracted CRO (b)(4). No issues.

Foreign Sites Italy and Germany-

2. Dr. Testori's inspection- Milano/Italy- Significant violations were noted. A 3-item Form FDA 483, Inspectional findings was issued to Dr. Testori..... A copy of the FDA 483 was provided the day I received it to Theresa and Max and discussed the significance of item 1 with a VAI/ or OAI classification pending final report. At this time insufficient information to make a determination of the significance of the findings... Therefore, I'm deferring the acceptability of item 1 on the FDA 483 to the review division to decide. Per my discussion with review division and per Max request I contacted the FDA investigator to get survival information of subjects and received the following:

- 14 subjects enrolled
- 6/7 records reviewed in detail
- 100% verified for informed consent and inclusion/exclusion criteria.
- All subjects died and the date from randomization till death not known at this time (may have some dates to be included in the report at a later date?)
- Only 2/14 subjects survived.

Per Max request I informed the FDA investigator to see if the investigator was able to verify survival information for each subject from the time of randomization till death on the current German inspection and to report to me as soon as possible. The Investigator agreed to do that. No additional information.

Question: We know an Imaging CRO was NOT used? Does the protocol mention that an imaging CRO or a charter was required?...No..... The observations may be significant.

3. Dr. Liquai's inspection- Mainz/Germany- Oral communication with FDA investigator stated no significant observations were noted. However, minor adverse events were found that were not reported. 12 subjects were enrolled and as of Wednesday 7 subjects are still alive. No additional information as of today to report. I contacted the investigator early today and have not heard from him yet.

4. Dr. Sosman' Inspection-Nashville- Significant improvement from previous inspections- No significant deficiencies noted in this current inspection- All data were verifiable- NAI classification

5. Dr. Margolin's Inspection -Seattle- No significant violations were noted. However, a 2-item Form 483 Inspectional findings was issued to Dr. Margolin who promised to respond to the observations within 15 days.

1. An investigation was not conducted in accordance with signed statement of investigation and investigational plan.
 - a. failure to identify, document, and report the subjects hair loss as an adverse event
 - b. concomitant NSAID medications for two subjects were not documented
 - c. lab test were not performed as required by the study protocol (oxygen Saturation and hematology/Serum Chemistry)
2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation
 - a. concomitant medications identified in the subjects diaries were not entered into the electronic case report forms

Additional observation was discussed with CI but not listed on the Form FDA 483 included discrepancies in data entries between the source document and what was recorded in the e-CRF. Clarification on the discrepancies was obtained from

the investigator and provided to the review division. The discrepancies appear to be insignificant.. Preliminary VAI classification.

As of today the Italian site appear to have a one item that may be significant and the division was advised of the observation and may wish to consider excluding the number of subjects(6/7) reviewed from the final analyses..... It is my understanding that a sensitivity analyses excluding the site was conducted with no Impact..

PLEASE NOTE: This is a preliminary summary based on e-mails /oral communications with FDA investigator/or FDA 483 items received as of today. Final and complete summary will be provided by Bob early next week

Take care and have a great weekend

Tony/for Bob

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Friday, July 22, 2011 10:11 AM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: FW: NDA 202429 vemurafenib CMC IR
Importance: High

[One more IR for response...](#)

From: Ferrara, Theresa
Sent: Wednesday, July 20, 2011 2:22 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib CMC IR
Importance: High

Dear Linda,
Please refer to NDA 202429, vemurafenib. Please respond to the following CMC question (listed below) no later than tomorrow morning (July 21st), 9am.

Please confirm if you will or will not be releasing to market the commercial batches submitted to the NDA ((b)(4)), which were manufactured in November 2010.

Thank you!
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA

07/22/2011

This communication was re-sent on Friday, July 22, 2011, to Linda Burdette at Roche, as Linda stated that original email communication sent on Wed. July 20, 2011 was not received.

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Friday, July 22, 2011 10:10 AM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: FW: NDA 202429 vemurafenib IR - non cutaneous SCC
Importance: High

Forwarding from Wednesday, July 22nd.

From: Ferrara, Theresa
Sent: Wednesday, July 20, 2011 1:46 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib IR - non cutaneous SCC
Importance: High

Dear Linda,
Please refer to NDA 202429 (vemurafenib). The review team has the following information request:

Please provide more information about the three patients on vemurafenib in the Phase 3 trial who were diagnosed with non-cutaneous squamous cell carcinomas. We are interested in location of the SCC, how it was discovered (monitoring or incidental finding) and how this informs your monitoring recommendations for non-cuSCCs in patients taking vemurafenib.

We are asking for a response back by 10am Friday, July 22nd, 2011.
Thank you.

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA

07/22/2011

This email communication was re-sent to Linda Burdette at Roche, as Linda stated original email communication sent Wed. July 20, 2011 was not received.

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Friday, July 22, 2011 10:06 AM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: FW: NDA 202429 vemurafenb - FDA revised PI sent 7.20.11
Importance: High
Attachments: NDA202429 PI.7.20.11.doc

Hi Linda,
See the attached. This is what I sent on Wednesday.

Theresa

From: Ferrara, Theresa
Sent: Wednesday, July 20, 2011 4:16 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenb - FDA revised PI sent 7.20.11
Importance: High

Dear Linda,
Please refer to NDA 202429 (vemurafenib) Zelboraf. Attached is the FDA-revised version of the PI. We ask that all changes be made using track-changes.

If you accept our proposed changes, then use the track-change function to accept those changes. If you have any revisions, then, please use track-changes so that we can see where the edits/modifications are made.

Our review is still ongoing, so, do not review section 17 of the PI.

Please return to me via email by Friday, July 22nd 11am. You do not need to submit this through the gateway at this time. Let me know if there are any questions.
Thank you!

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA

07/22/2011

this email communication was re-sent on July 22, 2011, as Linda Burdette stated that she did not receive original email communication

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Chemistry, Manufacturing and Controls Guidance

Meeting Date and Time: Tuesday, June 21, 2011 0900 – 1030 ET
Meeting Location: Teleconference

Application Number: NDA 202429
Product Name: Vemurafenib (R05185426)
Indication: BRAF^{v600} mutation-positive unresectable or metastatic melanoma
Sponsor/Applicant Name: Hoffman-La Roche Inc.

Meeting Chair: Haripada Sarker, PhD
Meeting Recorder: Deborah Mesmer, MS

FDA ATTENDEES

Office of New Drug Quality Assessment

Anne Marie Russell, PhD	Chemistry Reviewer (6 Jul 2011)
Haripada Sarker, PhD	CMC Lead
Deborah Mesmer, MS	Regulatory Health Project Manger for Quality (6 Jul 2011)
Deepika Arora Lakhani, PhD	Biopharmaceutics Reviewer
Angelica Dorantes	Biopharmaceutics Team Leader (6 Jul 2011)

DDOP

Amy Tilley	Regulatory Project Manager
------------	----------------------------

SPONSOR ATTENDEES

Duane Voss	Technical Regulatory Affairs – Nutley
David Ridge PhD	Technical Regulatory Affairs – Nutley
Richard Steinbach BPharm	Technical Regulatory Affairs – Nutley
Rina Gamboni PhD	Technical Regulatory Affairs – Basel
Fabian Schwarb PhD	Technical Regulatory Affairs – Basel
Larry Cain PhD	Technical Regulatory Affairs – Basel
Colm O'Mahony PhD	Technical Regulatory Affairs – Basel
Walfrido Antuch Garcia PhD	Technical Regulatory Affairs – Basel
Charles Meyer	Planning Commercial – Basel
Muriel Cordon Federspiel PhD	Analytical Development – Basel
Raman Iyer PhD	Pharmaceutical Development – Nutley
Duk Soon Choi PhD	Pharmaceutical Development – Nutley
Peter Luetolf PhD	Formulation Development – Basel
Anni Pabst Ravot PhD	Formulation Development – Basel
Paolo Marcarino PhD	Manufacturing – Segrate, Italy
Maria Angela Girometta PhD	Manufacturing – Segrate, Italy
Ralph Diodon PhD	Analytical Development – Basel

Hans-Juergen Mair PhD
Catrin Hartleif
Hansjorg Gruendler PhD

Chemical Process Development – Basel
Quality Assurance, Commercial – Basel
API Manufacturing – Basel

1.0 BACKGROUND

17-Jun-2011: FDA sent information request (IR) #2 to Roche, requested response by 24-Jun, and teleconference on 21-Jun to discuss plan to submit requested information.

2.0 DISCUSSION

2.1 Non-clinical materials: Provide a table listing all non-clinical studies conducted with the (b) (4). Include the batch number, of the (b) (4) used in the study and the type of study. Include batch analysis results for any batches not submitted in the NDA. Describe the material identified as RO5185426-007 in non-clinical study 103286 and provide batch analysis results. Describe how the impurities in all the non-clinical lots compare to the proposed specifications for RO5185426 and RO5185426-006, including differences in analytical methods (e.g. RRF), impurity identification (e.g. RRT) and levels.

Teleconference Discussion: Roche will provide requested information for all non-clinical safety studies by 24-Jun.

2.2 Drug Substance Manufacturing Process: In the absence of a master batch record for the drug substance manufacturing process, additional details are needed for Section 3.2.S.2.2 Description of the Manufacturing Process and Process Controls. (b) (4)

Since similar information is missing for each step in the synthesis, the following example lists in detail the needed information for Step (b) (4) to give an example of the level of detail required. Revise all steps to provide this level of detail for the manufacturing process. (b) (4)

(b) (4)



Teleconference Discussion: Roche will provide requested information by 24-Jun.

2.3 **Drug Product Manufacturing Process:** On review of the submitted master batch record for manufacture of the drug product (tableting/coating only) and Section 3.2.P.3.3 Description of the Manufacturing Process and Process Controls, additional details are needed.

2.3.1 Provide a Master Batch Record, in English, for the manufacturing of the drug product (b) (4)



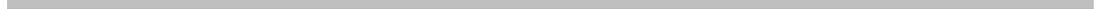
Teleconference Discussion: Roche will provide requested information by no later than 11-Jul. This date was to be confirmed by Roche

2.3.2 Revise Section 3.2.P.3.3 Description of the Manufacturing Process and Process Controls to include the following information:

(b) (4)



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(b) (4)



3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion at the conclusion of the meeting.

4.0 ACTION ITEMS

There are no other action items outside of those included in the discussion section (above).

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Chemist/Sr. Regulatory Health Project Manager - Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Deborah Mesmer, MS
Regulatory Health Project Manger for Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

{See appended electronic signature page}

Haripada Sarker, Ph.D.
Chief, Branch 2 (*acting*)
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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/s/

SCOTT N GOLDIE
07/08/2011

DEBORAH M MESMER
07/08/2011

HARIPADA SARKER
07/13/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, July 20, 2011 4:16 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenb - FDA revised PI sent 7.20.11
Importance: High
Attachments: NDA202429 PI.7.20.11.doc

Dear Linda,

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If you accept our proposed changes, then use the track-change function to accept those changes.

If you have any revisions, then, please use track-changes so that we can see where the edits/modifications are made.

Our review is still ongoing, so, do not review section 17 of the PI.

Please return to me via email by Friday, July 22nd 11am. You do not need to submit this through the gateway at this time. Let me know if there are any questions.

Thank you!

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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THERESA A FERRARA
07/20/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, July 20, 2011 2:22 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib CMC IR
Importance: High

Dear Linda,
Please refer to NDA 202429, vemurafenib. Please respond to the following CMC question (listed below) no later than tomorrow morning (July 21st), 9am.

Please confirm if you will or will not be releasing to market the commercial batches submitted to the NDA [REDACTED] (b) (4) which were manufactured in November 2010.

Thank you!
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
07/20/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, July 20, 2011 1:46 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib IR - non cutaneous SCC
Importance: High

Dear Linda,

Please refer to NDA 202429 (vemurafenib). The review team has the following information request:

Please provide more information about the three patients on vemurafenib in the Phase 3 trial who were diagnosed with non-cutaneous squamous cell carcinomas. We are interested in location of the SCC, how it was discovered (monitoring or incidental finding) and how this informs your monitoring recommendations for non-cuSCCs in patients taking vemurafenib.

We are asking for a response back by 10am Friday, July 22nd, 2011.

Thank you.

Theresa

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email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
07/20/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Monday, July 18, 2011 2:52 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 Zelboraf PMRs and PMCs

Dear Linda,

The review team has reviewed the PMRs and PMCs timeline for NDA 202429.

We would like to notify you that we will be modifying the timeline for the PMR listed below from 7 years to 5 years. Based on past experience with other examples, the Division feels that a timeline for completion in 5 years (2017) is more realistic.

Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of vemurafenib.

The timetable you submitted on July 12, 2011 states that you will conduct this trial according to the following timetable:

Protocol Submission: 05/01/2012

Final Protocol Submission: 09/14/2012

Trial Completion* Date: 02/15/2017

**PK primary objective*

Final Report and Datasets Submission: 08/15/2017

Please let me know if you have questions or anything is unclear. Thank you.

Sincerely,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
07/18/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Monday, July 18, 2011 9:55 AM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: RE: NDA 202429 Vemurafenib IR - NO25026 AE datasets (3 MSU) and PMCs/PMRs timeline

Dear Linda,
Thank you for sending me the PMR and PMC document.

However, we will need this to be made as an official submission to the NDA. Please submit formally thru the gateway. Thank you.

Sincerely,
Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Tuesday, July 12, 2011 11:47 AM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: RE: NDA 202429 Vemurafenib IR - NO25026 AE datasets (3 MSU) and PMCs/PMRs timeline

Hi Theresa,

First, please let Dr. McKee know that we are submitting the 3MSU AE datasets for NO25026 (BRIM3) through the gateway to NDA 202429. I am happy to provide also by email, but one of the files is ~11 MB, plus all the links between the define file and other documentation will be lost in email transmission. Let me know if you would also like the email version.

I've also attached our responses to the draft PMR and PMC document you sent on July 6. I made a few corrections for clarification in revisions mode. For example, I changed "Protocol Submission" to "Protocol Amendment Submission" to make sure the Division understands that our Phase 2 trial in papillary thyroid cancer is ongoing. Please let me know if the Division has any questions or needs clarifications on our responses.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

CONFIDENTIALITY NOTICE: This message is intended for the use of the named recipient(s) only and may contain confidential and/or proprietary information. If you are not the intended recipient, please contact the sender and delete this message. Any unauthorized use of the information contained in this message is prohibited. Thank you.

From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Wednesday, July 06, 2011 1:17 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Kacuba, Alice

Subject: FW: NDA 202429 Vemurafenib IR - PMCs/PMRs timeline

Importance: High

Dear Linda,

For NDA 202429, I want to clarify about the PMRs and PMCs, as Alice requested that I clarify what is being requested.

We are sharing the PMRs with you as a courtesy. Please provide a date to the PMRs.

Additionally, for the PMCs, you will need to respond in writing (written agreement to the dates). Please let me know if you have any concerns.

Please provide a response by Monday, July 11th 10am.

Thank you.

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

From: Ferrara, Theresa

Sent: Wednesday, July 06, 2011 12:39 PM

To: 'Burdette, Linda'

Cc: Tilley, Amy; Kacuba, Alice

Subject: NDA 202429 Vemurafenib IR - PMCs/PMRs timeline

Importance: High

Dear Linda,

Please find attached a timeline for the draft PMRs/PMCs for the review of Vemurafenib, NDA 202429.

Please provide responses and return to me via email by Monday, July 11th, 10am.

Thank you.

Best,

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
07/18/2011



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Chemistry, Manufacturing and Controls Guidance

Meeting Date and Time: Tuesday, July 12, 2011 1400 – 1430 ET
Meeting Location: Teleconference

Application Number: NDA 202429
Product Name: Vemurafenib (R05185426)
Indication: BRAF^{v600} mutation-positive unresectable or metastatic melanoma
Sponsor/Applicant Name: Hoffman-La Roche Inc.

Meeting Chair: Sarah Pope Miksinski, PhD
Meeting Recorder: Scott N. Goldie, PhD

FDA ATTENDEES

Office of New Drug Quality Assessment

Scott N. Goldie, PhD, Chemist/Sr. Regulatory Health Project Manger for Quality
Richard T. Lostritto, PhD, Director, Division of New Drug Quality Assessment I
Sarah Pope Miksinski, PhD, Chief, Branch 2
Anne Marie Russell, PhD, CMC Reviewer

Division of Drug Oncology Products

Theresa Ferrara, Regulatory Health Project Manager
Amna Ibrahim MD, Deputy Director
Robert Justice MD, Director
Alice Kacuba, Chief Regulatory Health Project Manager

SPONSOR ATTENDEES

Duane Voss	Technical Regulatory Affairs - Nutley
David Ridge PhD	Technical Regulatory Affairs - Nutley
Richard Steinbach BPharm	Technical Regulatory Affairs - Nutley
Nirdosh Jagota PhD	Technical Regulatory Affairs - Nutley
Rina Gamboni PhD	Technical Regulatory Affairs - Basel
Larry Cain PhD	Technical Regulatory Affairs - Basel
Walfrido Antuch Garcia PhD	Technical Regulatory Affairs - Basel
Anni Pabst Ravot PhD	Formulation Development - Basel
Hans-Juergen Mair PhD	Chemical Process Development - Basel
Catrin Hartleif	Quality Assurance, Commercial - Basel
Markus Deichmann PhD	Chemical Process Development - Basel
Alexander Glomme PhD	Process Validation - Segrate
Wolfgang Goehring PhD	Analytical Development - Basel

Christopher Bowden PhD
Linda Burdette, PhD
Paolo Marcarino PhD

Clinical Development - Nutley
Drug Regulatory Affairs - Nutley
Manufacturing - Segrate, Italy

1.0 BACKGROUND

The purpose of this teleconference is to gain agreement on the outstanding chemistry, manufacturing and controls deemed necessary to ensure the efficacy of the product.

2.0 DISCUSSION

- 2.1 Recommendation #1: For control of  (b) (4)

 acceptance testing.

To adequately address this recommendation: Submit the following documents as soon as possible, preferably within 24 hours:



To adequately address this recommendation: Submit the following documents as soon as possible, preferably within 24 hours:



(b) (4)



3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion at the conclusion of the meeting.

4.0 ACTION ITEMS

At the conclusion of the teleconference, Roche agreed to submit the agreed upon materials to fulfill all of FDA's recommendations without modification as soon as possible, preferably within 24 hours of the conclusion of the teleconference.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Chemist/Sr. Regulatory Health Project Manager - Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sarah Pope Miksinski, PhD,
Chief, Branch 2,
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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/s/

SCOTT N GOLDIE
07/12/2011

HARIPADA SARKER on behalf of SARAH P MIKSINSKI
07/12/2011

Ferrara, Theresa

From: Merchant, Lubna
Sent: Monday, July 11, 2011 1:24 PM
To: Ning, Yang-Min (Max); Ferrara, Theresa
Cc: Johnson, John R
Subject: Re: NDA 202429 - Status update

Max,

DMEPA did find the C and C labels submitted on 6/22 acceptable.

Thanks,
Lubna

From: Ning, Yang-Min (Max)
Sent: Monday, July 11, 2011 01:06 PM
To: Ferrara, Theresa
Cc: Merchant, Lubna; Johnson, John R
Subject: RE: NDA 202429 - Status update

Theresa,
No later than tomorrow as we need to meet our internal deadline regarding PMRs/Cs..

For the carton and container labeling, the previous responses were considered acceptable by the DMEPA. Lubna, could you confirm that?

I am not aware of the response tracker that Alice asked us to submit to the NDA. what is the purpose? please help me understand,

Max

From: Ferrara, Theresa
Sent: Monday, July 11, 2011 12:58 PM
To: Ning, Yang-Min (Max)
Subject: FW: NDA 202429 - Status update
Importance: High

Hi Max,
See email below from Linda.
We can talk later today.

Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Monday, July 11, 2011 11:58 AM
To: Ferrara, Theresa
Cc: Berkhin, Maria {PDR4~Nutley}
Subject: NDA 202429 - Status update

Theresa,

I spoke too quickly last week. We are holding additional meetings today to discuss one of the PMR PMC study timelines. I remain hopeful that I will be able to send tonight or latest tomorrow morning.

Could you also please check with the Review Division about whether or not they anticipate further changes to the carton/container labeling? We accepted the Division's recommendations and resubmitted the artwork to the NDA on June 23. The reason for this request is because we would like to initiate printing for the carton and container labeling, with the understanding that we are doing so at our own risk. However, it would be good to know if the Division is considering further changes to the carton/container labeling before initiating this activity.

Finally, regarding the response tracker that Alice asked us to submit to the NDA, should we be providing as a periodic update to the NDA? Do you want this as a cumulative tracker or to start with the responses not covered in the previous response tracker?

Thanks for your help with the above questions.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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/s/

THERESA A FERRARA
07/21/2011

Ferrara, Theresa

From: McKee, Amy
Sent: Friday, July 08, 2011 2:51 PM
To: 'Burdette, Linda'; Ferrara, Theresa
Cc: Voss, Duane {PT --Nutley}
Subject: RE: NDA 202429: 3MSU

Linda,

When I looked at the dataset titled Adverse Events (AE.xpt) in the submission that came through the eCTD on 6/30/11, there is no column for AE preferred term, just a column for the investigator text for the AE. I am trying to confirm the updated rates of AEs that were submitted in the 3MSU so that it can be updated in the label for the most accurate description of AEs possible.

Thanks,

Amy

Amy E. McKee, M.D.
Medical Officer
FDA/CDER/OND/OODP/DDOP
White Oak, Building 22 Room 5232
10903 New Hampshire Avenue
Silver Spring, MD 20993
(P) 301-796-3909
(F) 301-796-9849
amy.mckee@fda.hhs.gov

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Friday, July 08, 2011 2:44 PM
To: Ferrara, Theresa
Cc: McKee, Amy; Voss, Duane {PT --Nutley}
Subject: RE: NDA 202429: 3MSU

Hi Theresa,

Believe me, it hasn't been for lack of trying to get you this information!

I just received word that the AE (and demoext) datasets needed to generate the BRIM3 AE tables in the 3MSU will be available late Monday (July 11) . If they are small enough, I will email them to you and Amy while we complete the electronic processing to upload to the xml backbone of the eCTD for formal submission through the gateway. If they are too large for email, the earliest we could have them through the gateway is Tues, July 12.

Amy, our statisticians were a little concerned about your statement that you *"have used the AE.xpt dataset that was included in the 3MSU, but it does not contain all the information I need to update the AE rates for both the label and my review."*

Their concerns were two-fold: First, the datasets submitted with the efficacy update are not cleaned for safety beyond March 1, although the snapshot cutoff for efficacy is March 31. Second, the new AE datasets they are

preparing now (ie, those for the BRIM3 AE tables in the 3MSU) do not contain new variables. Can you please let us know what information was missing or what additional information would be helpful for your review so that we can make sure it is included in the datasets we plan to submit next week?

Theresa, I believe we will be on track to submit the timelines for the PMRs/PMCs on Monday as requested. Our last outstanding request from the CMC group (translated batch records) will also be submitted on Monday, as requested.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Friday, July 08, 2011 2:20 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: McKee, Amy
Subject: RE: NDA 202429: 3MSU

Hi Linda,
I just wanted to touch base with you on your expected timeline for submitting the dataset for the adverse events. When you have a time frame, please let me know.

Thank you.

Theresa

From: McKee, Amy
Sent: Thursday, July 07, 2011 2:45 PM
To: 'Burdette, Linda'
Cc: Ferrara, Theresa
Subject: RE: NDA 202429: 3MSU

No, no programming code required.

Thanks,

Amy

Amy E. McKee, M.D.
Medical Officer
FDA/CDER/OND/OODP/DDOP
White Oak, Building 22 Room 5232
10903 New Hampshire Avenue
Silver Spring, MD 20993

(P) 301-796-3909
(F) 301-796-9849
amy.mckee@fda.hhs.gov

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Thursday, July 07, 2011 2:42 PM
To: McKee, Amy
Cc: Ferrara, Theresa
Subject: RE: NDA 202429: 3MSU

Hi Amy,

Do you also need the programming code to generate summary AE tables? That question came up today because it will impact our timelines.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: McKee, Amy [mailto:Amy.McKee@fda.hhs.gov]
Sent: Thursday, July 07, 2011 2:04 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Ferrara, Theresa
Subject: RE: NDA 202429: 3MSU

Linda,

Just to clarify, I am hoping to receive an AE dataset with all the AEs reported in the NO20506 trial, including AEs from both the initial submission and from the 3MSU. I have used the AE.xpt dataset that was included in the 3MSU, but it does not contain all the information I need to update the AE rates for both the label and my review. Thanks again, and let me know if you have any questions about this request.

Amy

Amy E. McKee, M.D.
Medical Officer
FDA/CDER/OND/OODP/DDOP
White Oak, Building 22 Room 5232
10903 New Hampshire Avenue
Silver Spring, MD 20993

(P) 301-796-3909
(F) 301-796-9849
amy.mckee@fda.hhs.gov

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Wednesday, July 06, 2011 11:23 AM
To: McKee, Amy
Subject: RE: NDA 202429: 3MSU

Thanks Amy, I will forward this request immediately to the team.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: McKee, Amy [mailto:Amy.McKee@fda.hhs.gov]
Sent: Wednesday, July 06, 2011 11:21 AM
To: Burdette, Linda {PDR4~Nutley}
Cc: Ferrara, Theresa; Tilley, Amy
Subject: NDA 202429: 3MSU

Dr. Burdette,

I am reviewing the 3MSU and am requesting that you also submit the dataset for adverse events that support the tables submitted in the report.

Thank you,

Amy McKee

Amy E. McKee, M.D.
Medical Officer
FDA/CDER/OND/OODP/DDOP
White Oak, Building 22 Room 5232
10903 New Hampshire Avenue
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amy.mckee@fda.hhs.gov

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/s/

THERESA A FERRARA
07/12/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, July 06, 2011 1:27 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice; Tilley, Amy
Subject: RE: NDA 202429 Vemurafenib - FDA partially revised PI
Attachments: FDA response Section 12.3 Vemurafenib label .doc

Hi Linda,

We have the following responses to your request for clarifications regarding the PK sections of the vemurafenib PI:

Section 12.4:

- Please provide clarification for the statement, “(b) (4) largest mean change from baseline of (b) (4) ms (upper bound of the 2-sided 90% confidence interval of 14 (b) (4) ms) was observed at (b) (4) hours post-dose on **Day 15** (b) (4).” As we noted in the NDA, we considered the largest mean change from baseline was **15.1 ms** (upper 95% CI: 17.7 ms), which was observed in **cycle 6**.

FDA Response:

We will provide a detailed response next week, as the QT reviewer is currently on leave. This section of the PI (Section 12.4) may be finalized once you receive the response from the QT reviewer.

Section 12.3

- Distribution PK section: Please provide clarification for the statement, “The population apparent volume of distribution for vemurafenib in metastatic melanoma patients is estimated to be **106 L** (with (b) (4)% inter-patient variability). As provided in the population PK report (Table 10), the population apparent volume of distribution was estimated to be **91 L** (with **64.8%** inter-patient variability)
- Elimination PK section: Please provide clarification for the statement, “The population apparent clearance of vemurafenib in patients with metastatic melanoma is estimated to be **31** (b) (4) L/day (with (b) (4)% inter-patient variability).” As provided in the population PK report (Table 10), the population apparent clearance of vemurafenib in patients with metastatic melanoma was estimated to be **29.3 L/day** (with **31.9%** inter-patient variability).

FDA Response: Please see the attached Word document for a detailed response to clarify our changes to Section 12.3.

Thank you.

Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Tuesday, July 05, 2011 5:28 PM
To: Tilley, Amy
Cc: Ferrara, Theresa
Subject: RE: NDA 202429 Vemurafenib - FDA partially revised PI
Importance: High

Hi Amy,

Since Riche was closed on Friday, today was the first opportunity the team had to discuss FDA’s revisions to the US PI.

Before completing our response, we need to have a better understanding of some of the differences in numerical values cited in FDA's text. These sections include the following:

- Section 12.4: Please provide clarification for the statement, "(b) (4) largest mean change from baseline of (b) (4) ms (upper bound of the 2-sided 90% confidence interval of 14 (b) (4) ms) was observed at (b) (4) hours post-dose on Day 15 (b) (4)." As we noted in the NDA, we considered the largest mean change from baseline was 15.1 ms (upper 95% CI: 17.7 ms), which was observed in **cycle 6**.
- Section 12.3 (Distribution PK section): Please provide clarification for the statement, "The population apparent volume of distribution for vemurafenib in metastatic melanoma patients is estimated to be **106 L** (with (b) (4)% inter-patient variability). As provided in the population PK report (Table 10), the population apparent volume of distribution was estimated to be **91 L** (with **64.8%** inter-patient variability)
- Section 12.3 (Elimination PK section): Please provide clarification for the statement, "The population apparent clearance of vemurafenib in patients with metastatic melanoma is estimated to be **31 (b) (4) L/day** (with (b) (4)% inter-patient variability)." As provided in the population PK report (Table 10), the population apparent clearance of vemurafenib in patients with metastatic melanoma was estimated to be **29.3 L/day** (with **31.9%** inter-patient variability).

We will try very hard to meet the response deadline of July 7, but obviously, would need to receive these clarifications from you tomorrow to make this goal. Please call me on my cell ((b) (6)) if you need further clarification.

Thanks much for your help with this.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Tilley, Amy [mailto:AMY.TILLEY@fda.hhs.gov]
Sent: Thursday, June 30, 2011 5:15 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Ferrara, Theresa
Subject: NDA 202429 Vemurafenib - FDA partially revised PI
Importance: High

Linda,

Attached please find the FDA partially revised PI.

Please only review the sections that are **not** grayed out. Accept changes or provide your revisions/comments to the PI (**on this document only**) and email it back to myself and Theresa Ferrara **no later than 4 pm on July 7, 2011.**

You **do not** need to officially submit the PI through the Gateway a courtesy copy via email is sufficient at this time.

Also attached is a Word document which provides justification for the drug being classified as Pregnancy Category D.

Should you have any questions please contact me or Theresa Ferrara.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products,
CDER, FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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The difference in apparent clearance (CL/F) and apparent volume of distribution (V/F) between males and females can be explained by body weight. In the sponsor's model, body weight was not identified as a covariate, yet no physiological reason was available as to why gender was necessary as a covariate on both CL/F and V/F. Body weight was tested as a covariate on CL/F and V/F in an FDA revised model where gender was not a covariate on CL/F or V/F. The results indicate that body weight explains differences between genders and reduces inter-subject variability for individuals with low or high body weight.

1.1.1 Models

The sponsor's population PK model was revised based on the results of the reviewer's analysis of the population PK model. The FDA's revised model is presented herein and is used to determine the population mean PK parameters for the relevant label statements.

Revisions were only made to the sponsor's covariate model. The structural model was not changed. Gender was removed as a covariate on both CL/F and V/F. Body weight was included as a covariate on CL/F and V/F using the sponsor's base structural model. Power functions centering weight around 70 kg were used to describe the effect of body weight on CL/F and V/F. The exponents of these functions were estimated for both CL/F and V/F.

1.2 Results

1.2.1 Population PK

Figure 1 shows that for the sponsor's final model there appears to be a correlation between body weight and both CL/F and V/F of vemurafenib.

Figure 1. Sponsor's final model results of inter-individual variation versus body weight suggest that weight may be a covariate for CL/F and V/F.

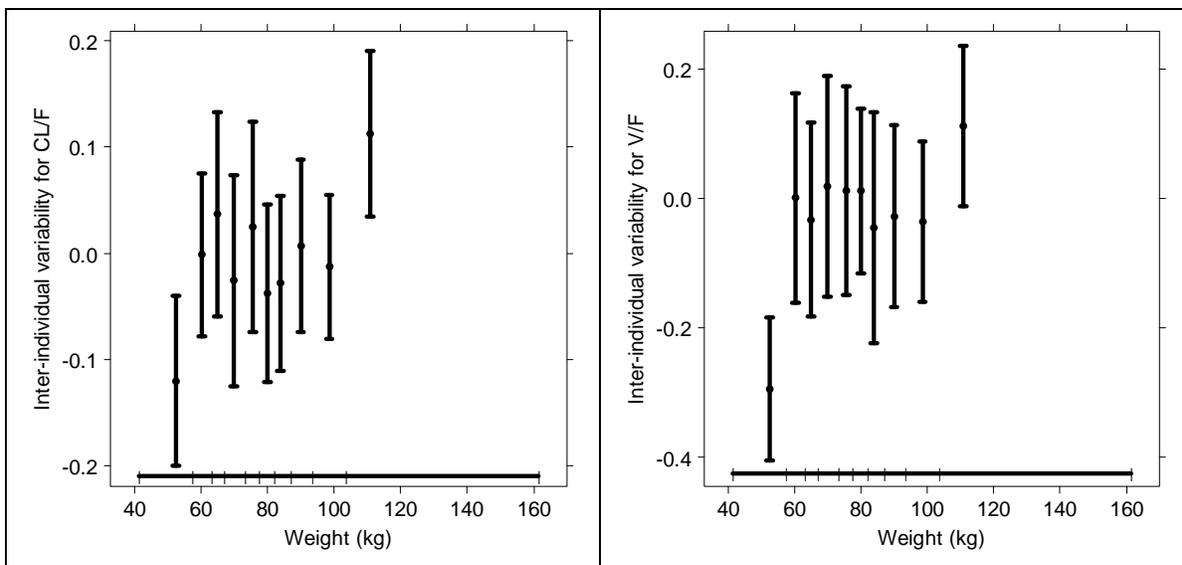


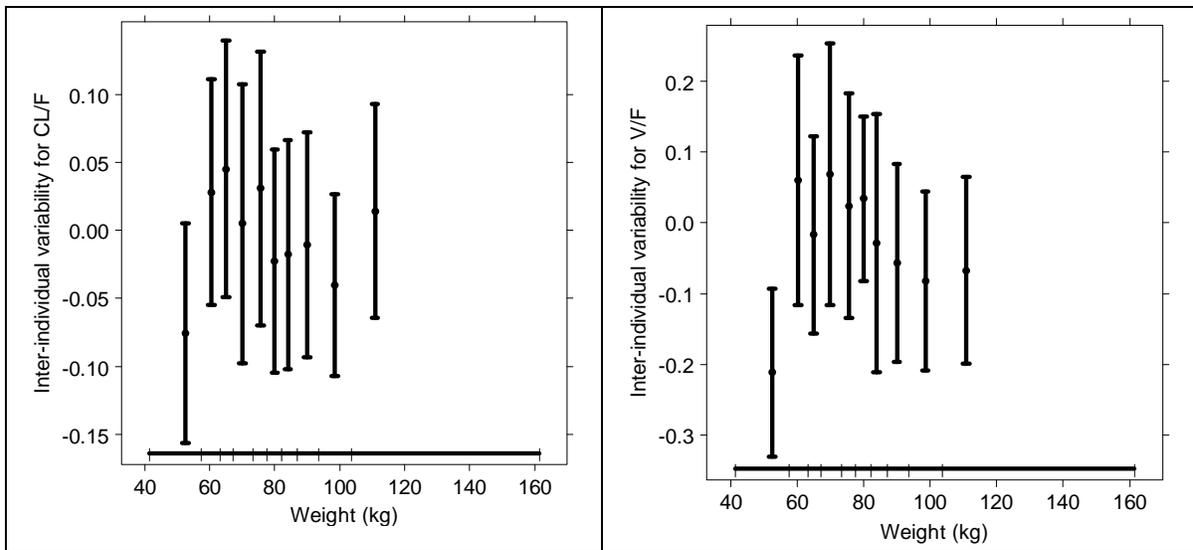
Table 1 and Figure 2 show the parameter estimates and results for the revised model with body weight as covariate instead of gender on both CL/F and V/F. The results indicate

reduced inter-subject variability for CL/F and V/F with body weight compared to the sponsor's model (Figure 2).

Table 1. Parameter estimates for final FDA revised model.

Parameter	Estimate	%RSE
Structural Model		
CL/F (L/day)	31.2	1.96
V/F (L)	106	6.65
Ka (1/day)	4.51	9.71
F1, Phase 1 & 2, Day 1-14	0.789	2.83
F1, Phase 1 & 2, Cycle 1, day 15 - Cycle 4	0.899	1.82
Covariate Model		
WT_CL	0.319	20.9
WT_V	0.740	20.4
IIV (%CV)		
CL/F	31.9	15.2
V/F	65.7	19.5
Ka	101	18.7
Residual Error		
Additive	0.814	9.05
Proportional (%)	22.8	2.70

Figure 2. Inter-individual variation versus body weight plots for the revised model show less correlation with body weight than the sponsor's final model. (Note: the scales are different between Figure 1 and Figure 2)



The inter-individual variability for CL/F (Figure 3) and V/F (Figure 4) by gender for the FDA revised model is similar to that for the sponsors final model.

Figure 3. Body weight as a covariate on vemurafenib CL/F explains differences in CL/F between males and females.

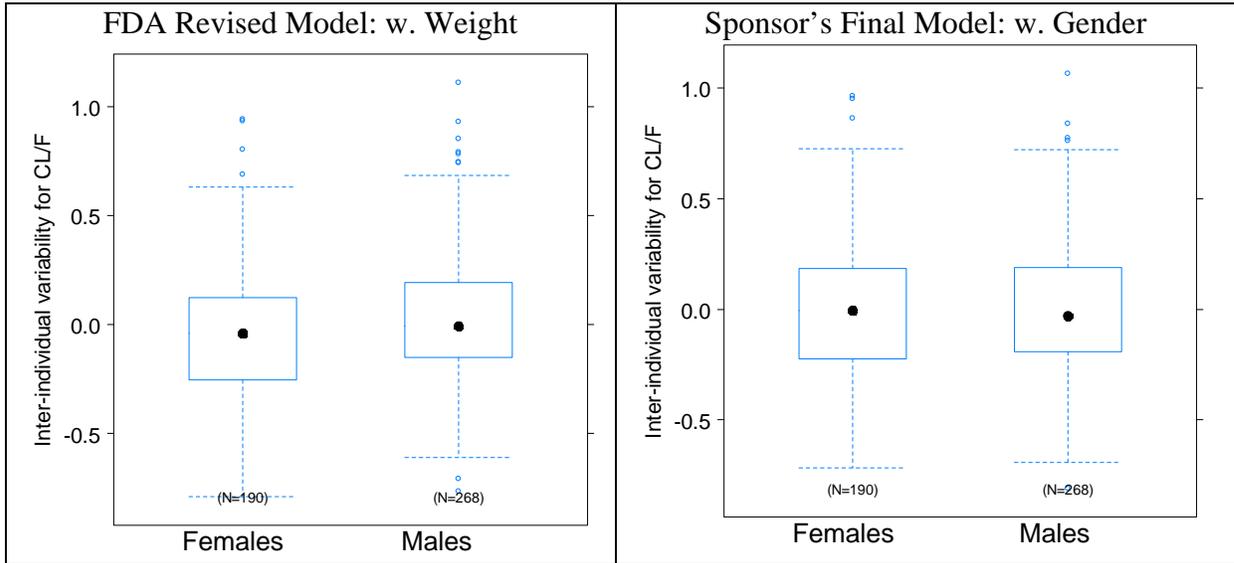
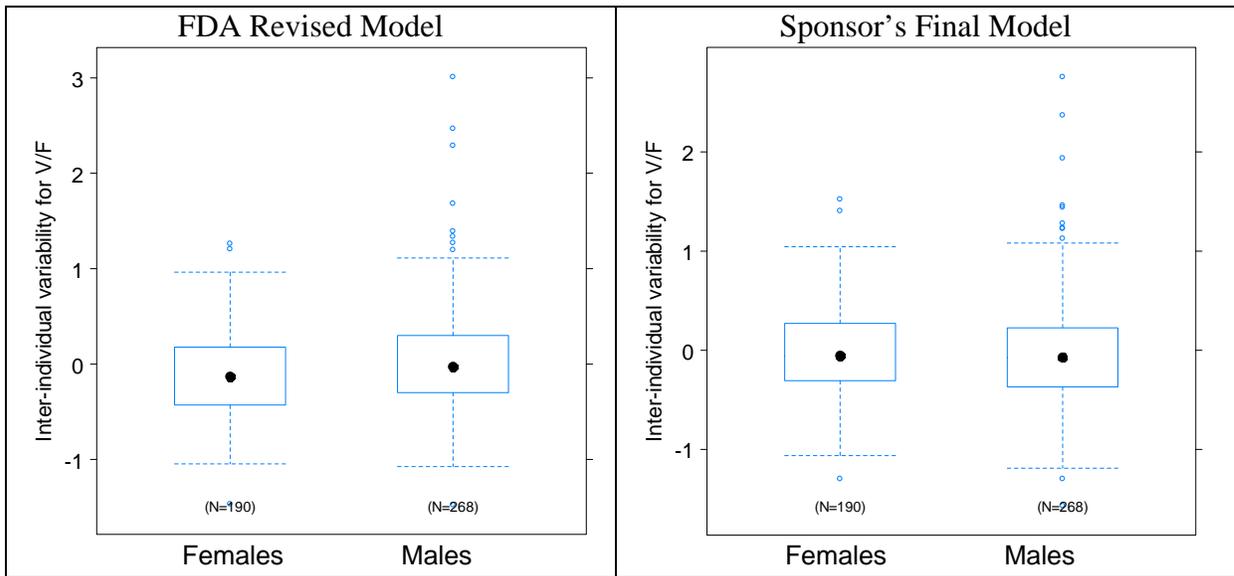


Figure 4. Body weight as a covariate on vemurafenib V/F explains differences in V/F between males and females.



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/s/

THERESA A FERRARA
07/06/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, July 06, 2011 1:17 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: FW: NDA 202429 Vemurafenib IR - PMCs/PMRs timeline
Importance: High
Attachments: Updated Draft PMRs-PMCs Inquiries for Vemurafenib 07062011 (2).doc

Dear Linda,
For NDA 202429, I want to clarify about the PMRs and PMCs, as Alice requested that I clarify what is being requested.

We are sharing the PMRs with you as a courtesy. Please provide a date to the PMRs.

Additionally, for the PMCs, you will need to respond in writing (written agreement to the dates). Please let me know if you have any concerns.

Please provide a response by Monday, July 11th 10am.

Thank you.
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

From: Ferrara, Theresa
Sent: Wednesday, July 06, 2011 12:39 PM
To: 'Burdette, Linda'
Cc: Tilley, Amy; Kacuba, Alice
Subject: NDA 202429 Vemurafenib IR - PMCs/PMRs timeline
Importance: High

Dear Linda,
Please find attached a timeline for the draft PMRs/PMCs for the review of Vemurafenib, NDA 202429.
Please provide responses and return to me via email by Monday, July 11th, 10am.

Thank you.

Best,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
07/06/2011

Tilley, Amy

From: Tilley, Amy
Sent: Thursday, June 30, 2011 5:15 PM
To: 'Burdette, Linda'
Cc: Ferrara, Theresa
Subject: NDA 202429 Vemurafenib - FDA partially revised PI

Importance: High

Follow Up Flag: Follow up
Due By: Thursday, July 07, 2011 4:00 PM
Flag Status: Flagged

Attachments: FDA revised PI sent to spon 6-30-11 NDA202429 vemurafenib proposed-PI TF 6-30-11.doc;
Justification for pregnancy Cat D.doc

Linda,

Attached please find the FDA partially revised PI.



FDA revised PI sent
to spon 6-...

Please only review the sections that are **not** grayed out. Accept changes or provide your revisions/comments to the PI (**on this document only**) and email it back to myself and Theresa Ferrara **no later than 4 pm on July 7, 2011.**

You **do not** need to officially submit the PI through the Gateway a courtesy copy via email is sufficient at this time.

Also attached is a Word document which provides justification for the drug being classified as Pregnancy Category D.



Justification for
pregnancy Ca...

Should you have any questions please contact me or Theresa Ferrara.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER,
FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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

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/s/

AMY R TILLEY
06/30/2011



NDA 202429

INFORMATION REQUEST

Hoffman-La Roche Inc.
Attention: Duane Voss
Program Director, Technical Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Voss:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vemurafenib (R05185426) 240 mg tablets.

We also refer to your 31 March, 27 May, 01 and 16 June 2011 submissions, containing Chemistry, Manufacturing and Controls drug substance and drug product quality information.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response to all items by **24 June 2011**, and a description of your plan to respond to these items at the teleconference scheduled for June 21, 2011, in order to continue our evaluation of your NDA.

1. Non-clinical materials: Provide a table listing all non-clinical studies conducted with the [REDACTED] (b)(4). Include the batch number, of the [REDACTED] (b)(4) used in the study and the type of study. Include batch analysis results for any batches not submitted in the NDA. Describe the material identified as RO5185426-007 in non-clinical study 103286 and provide batch analysis results. Describe how the impurities in all the non-clinical lots compare to the proposed specifications for RO5185426 and RO5185426-006, including differences in analytical methods (e.g. RRF), impurity identification (e.g. RRT) and levels.
2. Drug Substance Manufacturing Process: In the absence of a master batch record for the drug substance manufacturing process, additional details are needed for Section 3.2.S.2.2 *Description of the Manufacturing Process and Process Controls*. [REDACTED] (b)(4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

If you have any questions, call Scott N. Goldie, Ph.D., Senior Regulatory Project Manager for Quality at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Haripada Sarker, Ph.D.
Chief, Branch II (*acting*)
Division of New Drug Quality Assessment 1
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

HARIPADA SARKER
06/17/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Friday, June 17, 2011 10:53 AM
To: 'Burdette, Linda'
Cc: Kacuba, Alice; Tilley, Amy; 'Berkhin, Maria'
Subject: NDA 202429 Zelboraf Clinical IR sent 6/17/11
Importance: High

Dear Linda,

Please refer to NDA 202429 Zelboraf (vemurafenib). We have the following clinical information requests, listed below:

1. Please provide an update on your planned "optional tumor biopsies" at baseline and at time of disease progression of study NO25026 (Appendix 8 of the clinical protocol). Specifically, how many biopsies have been performed thus far in the Phase 3 trial, and how many total biopsies do you anticipate gathering from all trials you have conducted?
2. Please provide an update on all your current open clinical protocols with Zelboraf. Please also specify clinical protocols that are planned to be open in the next year, regardless of disease types.

Please respond by next Friday, June 24, 2011. Let us know if there are any questions. Thank you.

Best regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
06/17/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Friday, June 10, 2011 5:03 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 (vemurafenib) carton & container comments

Dear Linda,
Please refer to NDA 202429 (vemurafenib). I have some comments for you regarding the carton and container labeling. Please see below. Please provide a response by Thursday, July 7th, 2011. Thank you.

A. General comments

We remind the Applicant of their requirement to comply with 21 CFR 208.24. We acknowledge the use of a Medication Guide statement. Please ensure that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose.

B. Proposed Container Label

1. Since the tablets are available in unit of use containers (15 days supply) and may be dispensed directly to patients, we recommend the addition of a statement "Do not crush or chew tablet" above the Rx only statement.
2. Relocate the "Each tablet contains..." statement to the side panel in order to decrease the clutter on the principal display panel.

3. The company symbol  Daiichi-Sankyo may be misinterpreted as the tablet image and should be deleted or relocated to the side panel.

C. Proposed Carton Labeling

1. See comment B1, B2 and B3.
2. Relocate the medication guide statement to appear below the Rx only statement as presented on the container label.
3. It is unclear what the oval graphic below the net quantity statement represents. The graphic should be deleted or replaced with the actual image of the tablet.

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
06/10/2011

Goldie, Scott

From: Goldie, Scott
Sent: Friday, June 10, 2011 2:57 PM
To: 'Voss, Duane'
Subject: RE: NDA202429 - Vemurafenib Tablets 240 mg

Hi Duane:

[Here is the clarification you requested:](#)

For the clarification on Question #5:

Your revision in response to Question #5, received June 1, 2011, is not acceptable as it does not provide a sufficiently specific unique identifier for the test method that allows clear reference to the method description in the NDA. Today, in lieu of a test method identification number, you propose a hyperlink to the specific test method for each attribute. This is acceptable provided that these links are listed in a separate column identified as the Test Method and link to the specific test for the attribute, and not just the section of the NDA containing the test methods. In this manner, revise the specifications for the drug substance, drug product, drug product intermediate and the starting material (b) (4).

[A response to this and the other outstanding points received by 14 June would be very helpful, as time is of the utmost importance at this point in the review cycle.](#)

Thank you,

Scott

From: Voss, Duane [mailto:duane.voss@roche.com]
Sent: Friday, June 10, 2011 2:07 PM
To: Goldie, Scott
Subject: NDA202429 - Vemurafenib Tablets 240 mg

Dear Scott,

We have a question that I hope you can help us with regarding the further clarifications that you sent to us on May 31, 2011. Because they came to us the day before we sent our responses to the May 20, 2011 questions, we are not certain if our response to question #5 (revising specifications to include reference to the test methods in the NDA) is acceptable. In our response, we explained that the laboratory-based documents contain both the specifications and the analytical methods.

The FDA clarification stated that a "sufficiently specific unique identifier (e.g. test method ID number) for the test method that allows clear reference to the method

description provided in the NDA." The information for specifications was placed in the section of the eCTD structure as required, and the methods were likewise in the corresponding leaf (e.g. Tablet test specifications are 3.2.P.5.1, and the corresponding methods are in 3.2.P.5.2). We can link each test in P.5.1 to its method in P.5.2 if that would be helpful for the review. We would appreciate any guidance that can be provided if additional information is needed for question 5.

We expect to have final responses to clarifications for #3 and #6 during the week of June 13. Thank you and your team for any further clarification that can be provided.

Best regards,

Duane

Duane Voss

Program Director, Drug Regulatory Affairs

Roche

(973) 562-3519 phone

(973) 562-3700 fax

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/s/

SCOTT N GOLDIE
06/10/2011

Ferrara, Theresa

From: Fourie Zirkelbach, Jeanne
Sent: Thursday, June 09, 2011 5:01 PM
To: 'Burdette, Linda'
Cc: Liu, Qi (CDER); Ferrara, Theresa
Subject: RE: NDA 202429 vemurafenib (BRAF inhibitor) IR from Clinical Pharmacology reviewer

Dear Linda,

We would like to request any information you have on how vemurafenib was administered in the phase 3 trial to assess the possible effect of food on exposure. It would be informative for us to know if investigators or patients reported administration mostly in a fasted state, or mostly in a fed state?

Could you please address this question as soon as possible.

Thank you,
Jeanne

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/s/

THERESA A FERRARA
06/10/2011



NDA 202429

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

ATTENTION: Matthew Klimek, PharmD
Program Manager, Regulatory Affairs

Dear Dr. Klimek:

Please refer to your New Drug Application (NDA) dated April 27, 2011, received April 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vemurafenib Tablets, 240 mg.

We also refer to your April 28, 2011 correspondence, received April 28, 2011, requesting review of your proposed proprietary name, Zelboraf. We have completed our review of the proposed proprietary name, Zelboraf and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your April 28, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Simon, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5205. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Theresa Ferrara at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/08/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, June 08, 2011 1:16 PM
To: 'Burdette, Linda'
Cc: Skarupa, Lisa; Kacuba, Alice
Subject: RE: NDA 202429: Request for Feedback on Phase 3 OS Update Proposal
Importance: High

Dear Linda,
Thank you for the update you have provided. The team has reviewed the table provided below, and accepts the OS update proposal containing **199 events**, using the clinical cutoff date of March 31st.

When the updated datasets are available, please send me courtesy email in advance of their submission. Thank you.

Sincerely,
Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Friday, June 03, 2011 11:51 AM
To: Ferrara, Theresa
Cc: Skarupa, Lisa; Kacuba, Alice
Subject: NDA 202429: Request for Feedback on Phase 3 OS Update Proposal
Importance: High

Dear Theresa,

At the teleconference on May 27, 2011, the Division asked Roche to provide another OS update of the Phase 3 NO25026 trial, with datasets, to be submitted by June 30, 2011. Roche proposed a clinical cutoff for the analysis of April 30, 2011, but could not confirm submission timelines at the teleconference until an assessment of an upcoming database snapshot was made.

Based on an assessment of the June 1 database snapshot, Roche confirms that we can submit an OS update by **June 30**. However, this proposal is predicated on using an earlier clinical cutoff date of March 31 than the April 30 cutoff proposed at the teleconference. In the assessment of the June 1 database snapshot (see table below), followup was defined as the percentage of patients/treatment group with followup within 90 days of the March and April cutoff dates. During followup, the visit assessment schedule is every 12 weeks (ie, ~90 days).

The preferred earlier clinical cutoff date of March 31 is based on more complete and balanced followup between the two treatment arms compared to the originally proposed April 30 clinical cutoff. In addition, the median followup is more than 6 months in the vemurafenib arm, which approximates the median followup of Phase 2 trial, NP22657. Finally, the March 31 cutoff date would not require additional database cleaning that would be recommended for the April 30 clinical cutoff, the latter of which would delay the submission of the OS update until July 21.

Comparison of NO25026 OS Followup based on March 31 and April 30 Clinical Cutoff Dates (June 1 database snapshot)

	March 31		April 30	
	Vemurafenib	DTIC	Vemurafenib	DTIC
n 90 days of cutoff date	96%	93%	94%	86%

	6.2	4.5	6.4	4.9
	199		211	
	June 30		July 21	

For these reasons, we consider the proposal of an OS update based on a clinical cutoff date of March 31, 2011 to meet the Division's request in terms of OS followup, data quality and submission timelines. We would appreciate the Division's feedback on this proposal as soon as possible so that data analysis and dataset preparations can be initiated.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Thursday, June 02, 2011 5:08 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Skarupa, Lisa; Kacuba, Alice
Subject: RE: information update on action items

Hi Linda,
I know the intention is to let the Agency know by tomorrow COB about the timeline for OS update with the dataset. I am going to be out of the office tomorrow. My colleague, Lisa Skarupa, will be covering for me. Please be sure to copy her and Alice on any communication about the estimated timelines.

Thanks again for all your help and cooperation.
Have a good evening.

Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Wednesday, June 01, 2011 6:25 PM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: information update on action items

Hi Theresa,

This is just a quick information update.

At the TC last Friday afternoon, we promised to get back to the Division this week with estimated timelines for conducting a later OS update on our Phase 3 trial. Although the assessment of database cleaning etc required for the analysis is taking a longer than what we originally thought, we are working on this and remain hopeful that we will be able to communicate a timeline to the Agency before your close of business on Friday.

We also received the response to the request for information on the mutation test results by the companion diagnostic test, Sanger sequencing and pyrosequencing from our diagnostic colleagues on the West Coast – however, too late to make it through the gateway today. The response will be submitted tomorrow, and I will forward to you by email as well. According to my records, that should close out all of the outstanding requests for information.

Have a good night.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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/s/

THERESA A FERRARA
06/08/2011

Ferrara, Theresa

From: Fourie Zirkelbach, Jeanne
Sent: Wednesday, June 08, 2011 10:19 AM
To: 'Burdette, Linda'
Cc: Ferrara, Theresa
Subject: RE: NDA 202429 vemurafenib (BRAF inhibitor) IR from Clinical Pharmacology reviewer

Linda,
Just a minor additional clarification. The ratios calculated should be the geometric mean ratios for the test/reference for AUC and Cmax.

Thank you,
Jeanne

From: Fourie Zirkelbach, Jeanne
Sent: Wednesday, June 08, 2011 10:12 AM
To: 'Burdette, Linda'
Cc: Liu, Qi (CDER); Ferrara, Theresa
Subject: RE: NDA 202429 vemurafenib (BRAF inhibitor) IR from Clinical Pharmacology reviewer

Dear Linda,

Regarding your study report NP22676:

It appears that the analysis conducted to determine the equivalence of the extent of exposure (AUC) and Cmax for each of the probe substrates before and after treatment of vemurafenib was done by using the geometric mean ratios of the probe drug/metabolite ratio with and without vemurafenib. If these ratios were within the equivalence boundary (0.8-1.25) then it was concluded that there was no interaction between vemurafenib and the respective probe substrates.

The above analysis is not how we typically assess the potential for drug-drug interactions. Can you please conduct an analysis by calculating the geometric mean ratios of just the parent probe substrate (not the parent/metabolite ratio) before and after treatment with vemurafenib. Can you also calculate the 90% confidence intervals for these ratios. This will be used to determine whether there is an interaction between the probe substrate and vemurafenib. Can you please conduct this analysis for all of the probe substrates

The above analysis is urgent for labeling purposes, and we would appreciate receiving the results as soon as possible.

Thank you,

Jeanne

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/s/

THERESA A FERRARA
06/08/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Thursday, June 02, 2011 5:07 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: RE: NDA 202429 vemurafenib - clinical IR
Attachments: NDA 202429 No Filing Issues Identified FINAL 6 2 11 (cor-ndafile-05) (2).pdf

Dear Linda,
Yes – I do have the written communication of the NDA filing! The application will officially be filed 60 days following the NDA receipt date.

You will also receive a hard copy of this letter through the mail.

Best regards,
Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Thursday, June 02, 2011 12:41 PM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: RE: NDA 202429 vemurafenib - clinical IR

Theresa –

I have a quick question for you. We were delighted to hear last Friday from Dr. Johnson that NDA 202429 had been filed and that the application had been granted priority review. I have folks on my side clamoring to know when we would receive written notification. Do you have a time frame yet when we would receive the letter?

Thanks in advance for any help you can provide.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Thursday, June 02, 2011 11:33 AM
To: Burdette, Linda {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: RE: NDA 202429 vemurafenib - clinical IR

Good Morning Linda,
Thank you. I will get this to the reviewers.

Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Thursday, June 02, 2011 11:31 AM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: RE: NDA 202429 vemurafenib - clinical IR

Hi Theresa,

Please find attached the response to the below request for information regarding mutation test results obtained with the cobas® 4800 BRAF V600 Mutation Test, Sanger sequencing and pyrosequencing methods. This response has also been formally submitted through the gateway to NDA 202429.

I decided to stay home from ASCO this week, so am available if there are any questions or need for further clarification.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
Director, PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Tuesday, May 24, 2011 3:00 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib - clinical IR
Importance: High

Dear Linda,
For review of NDA 202429 (vemurafenib), we have the following clinical information request below. Please provide us a response as soon as possible.
Thank you.

According to the CSR, "Sanger sequencing has limited sensitivity for somatic mutation detection, with loss of sensitivity when mutation levels fall below ~20-30%, as compared with the estimated sensitivity of 5% for the cobas test. Thus it was expected that the cobas test would identify mutations that Sanger sequencing would not detect. Furthermore we observed a test failure rate of approximately 10% for Sanger sequencing in the samples from the Phase 2 study, NP22657, as compared to a test failure rate of < 1% for the cobas test."

Please submit:

- 1) Provide the % mutation for each sample tested as determined by pyrosequencing data or otherwise, the % tumor proportion for each sample as determined by the pathologist(s), and all other pertinent information regarding mutation levels for patients enrolled on the Phase 2 and Phase 3 studies. If possible, the data submission should have the PROTO, USUBJID, % tumor proportion of sample and % mutation levels for all patients in which mutation levels were determined.
- 2) Indicate the specific mutation results (E, K, D, R, EE, etc) for each sample, both cobas test negative and cobas test positive) as determined by the cobas test, Sanger sequencing, and pyrosequencing. This information should include data from patients who had a negative cobas test who subsequently had sanger sequencing and/or 454 pyrosequencing which was used to determine the sensitivity, specificity, positive and negative predicitive values for the cobas test.

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848



NDA 202429

FILING COMMUNICATION

Hoffman-La Roche
Attention: Linda Burdette, Ph.D.
Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Burdette:

Please refer to your New Drug Application (NDA) dated April 27, 2011, received April 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Zelboraf (vemurafenib) tablets, 240 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is October 28, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 23, 2011.

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

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 Theresa Ferrara, Regulatory Project Manager, at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.Sc.
Director, Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ALICE KACUBA
06/02/2011
Signing for Dr. Justice.

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/s/

THERESA A FERRARA
06/02/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Thursday, June 02, 2011 11:59 AM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: RE: NDA 202429 vemurafenib - clinical IR

Hi Linda,
Thank you for your submission.

Can you also send us the data used to generate the pdfs in a SAS transport file (.xpt format)?

Thanks.
Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Thursday, June 02, 2011 11:31 AM
To: Ferrara, Theresa
Cc: Kacuba, Alice
Subject: RE: NDA 202429 vemurafenib - clinical IR

Hi Theresa,

Please find attached the response to the below request for information regarding mutation test results obtained with the cobas[®] 4800 BRAF V600 Mutation Test, Sanger sequencing and pyrosequencing methods. This response has also been formally submitted through the gateway to NDA 202429.

I decided to stay home from ASCO this week, so am available if there are any questions or need for further clarification.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
Director, PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Tuesday, May 24, 2011 3:00 PM
To: Burdette, Linda {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: NDA 202429 vemurafenib - clinical IR
Importance: High

Dear Linda,

For review of NDA 202429 (vemurafenib), we have the following clinical information request below. Please provide us a response as soon as possible.

Thank you.

According to the CSR, "Sanger sequencing has limited sensitivity for somatic mutation detection, with loss of sensitivity when mutation levels fall below ~20-30%, as compared with the estimated sensitivity of 5% for the cobas test. Thus it was expected that the cobas test would identify mutations that Sanger sequencing would not detect. Furthermore we observed a test failure rate of approximately 10% for Sanger sequencing in the samples from the Phase 2 study, NP22657, as compared to a test failure rate of < 1% for the cobas test."

Please submit:

- 1) Provide the % mutation for each sample tested as determined by pyrosequencing data or otherwise, the % tumor proportion for each sample as determined by the pathologist(s), and all other pertinent information regarding mutation levels for patients enrolled on the Phase 2 and Phase 3 studies. If possible, the data submission should have the PROTO, USUBJID, % tumor proportion of sample and % mutation levels for all patients in which mutation levels were determined.
- 2) Indicate the specific mutation results (E, K, D, R, EE, etc) for each sample, both cobas test negative and cobas test positive) as determined by the cobas test, Sanger sequencing, and pyrosequencing. This information should include data from patients who had a negative cobas test who subsequently had sanger sequencing and/or 454 pyrosequencing which was used to determine the sensitivity, specificity, positive and negative predictive values for the cobas test.

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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THERESA A FERRARA
06/02/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Tuesday, May 31, 2011 6:35 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice
Subject: NDA 202429 animal cuSCC study - IR

Hi Linda,
Please refer to NDA 202429 (vemurafenib). The Agency is requesting the updated non-clinical cuSCC study (HRAS mutation study) by mid-June.
Please let me know a targeted submission date for this animal study.

Thank you.

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
05/31/2011

Goldie, Scott

From: Goldie, Scott
Sent: Tuesday, May 31, 2011 4:36 PM
To: 'Voss, Duane'
Subject: FW: NDA202429 - Vemurafenib Tablets 240 mg

Duane:

Here are the clarifications (in red color below) that you requested regarding our information request of 20 May. We understand that you may need additional time to respond to these clarification statements and may change your interpretation/submissions in response to our information requests, but please respond to these as soon as possible.

If you have any further questions, please do not hesitate to contact me.

Scott

Dear Scott,

This morning, the CMC team reviewed and discussed the Information Request you sent to us on Friday. We are hoping your team can clarify a few questions that resulted from our discussions:

Question 3: Regarding a detailed description of (b) (4) step, the "i.e." contained in the request is basically the same language as we already have at each step, (b) (4)
(b) (4) This statement already appears at the top of page 4/8 in 3.2.S.2.2. So, we are not certain what more is required, especially since in accordance with ICHQ7A, reprocessing is allowed, and can be performed even if it is not specifically stated in the NDA.

To clarify our request:

a) Drug Substance:

(b) (4)

b) Drug Product:

(b) (4)

(b) (4)

Format question: Would it be acceptable to submit the responses to this Information Request in Module 1, Section 1.11.1 Quality Information Amendment, keeping the responses focused on just submitting the information requested? As an example, the request to revise all specifications to include the test method used would mean that 1 page in the 55-page document in 3.2.P.3.4 needs revision. Can we just submit the new specification page as part of the responses in 1.11.1 or must we revise the one page in the 55-page document and re-submit 55 pages in 3.2.P.3.4?

Submit revised versions of NDA material to the original section of the NDA. The electronic format allows for the tracking of versions. Submit new material to the pertinent section of the NDA. It would be helpful for you to also submit your response to an Information Request to the proposed Section 1.11.1, which links to the revised tables, specifications, etc located throughout the NDA. This will aid the review

Thank you for any clarifications that you can provide!

Best regards,

Duane

Duane Voss
Program Director, Drug Regulatory Affairs
Roche
(973) 562-3519 phone
(973) 562-3700 fax

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/s/

SCOTT N GOLDIE
05/31/2011

MEMORANDUM OF TELECON

DATE: May 27, 2011

APPLICATION NUMBER: NDA 202429 Vemurafenib

BETWEEN:

Name: Linda Burdette, Ph.D.
Phone: (b) (4)
Representing: Hoffman-La Roche

AND

Name: Amy Tilley
DDOP HFD-150

SUBJECT: Clarification of earliest submission dates for Safety Information

- What is the earliest time Roche can submit the 3-m safety update? We'd like to have that submitted by the end of June.

TCON Discussion:

The sponsor stated they could submit the 3-m safety update by the end of June.

- What is the earliest time to submit an updated survival analysis or the final survival analysis along with its dataset?

TCON Discussion:

The sponsor stated they could submit the updated OS with datasets by the end of June. Sponsor also stated they will notify us early next week with an exact date. Updated datasets will also be submitted along with the patient cross over information.

- In the presentation, the proposed survival data cutoff was March 1, 2011. What would be the latest data cut-off time for survival Roche could provide?

TCON Discussion:

The agreed upon cut off date will be April 30th 2011, with an estimation of 214 deaths. The sponsor will provide both the raw and derived datasets for survival. Also the sponsor will submit the eCRFs and pathological review report for de novo melanomas.

Amy Tilley
Regulatory Project Manager

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/s/

AMY R TILLEY
05/27/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Wednesday, May 25, 2011 5:04 PM
To: 'Burdette, Linda'
Subject: NDA 202429 vemurafenib t-con questions for consideration
Importance: High

Dear Linda,

To help prepare for our tele-conference on Friday, we have a few requests that we ask Roche to consider.

First, the FDA would like to take an early action and your cooperation is greatly appreciated. This will require earlier submission of the safety update and updated survival analysis than the July 26, 2011 date that was proposed in your presentation on May 23, 2011. It will also require very rapid responses from Roche to the FDA queries during the review. Thus, we ask you to consider the following questions:

- What is the earliest time Roche can submit the 3-m safety update? We'd like to have that submitted by the end of June.
- What is the earliest time to submit an updated survival analysis or the final survival analysis along with its dataset? In the presentation, the proposed survival data cutoff was March 1, 2011. What would be the latest data cut-off time for survival Roche could provide? Based on the number of new events occurring from the interim analysis (conducted in December 2010) to March 1, 2011, we estimated that the events required for the final survival analysis could have been reached by now.

Thank you for your assistance during the review of your application.

Best regards,
Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Wednesday, May 25, 2011 11:28 AM
To: Ferrara, Theresa
Subject: RE: NDA 202429 vemurafenib t-con proposed time- Friday May 27, 3:30pm?

Hi Theresa,

Our team members are available for a short TC with the Division on Friday, May 27 at 3:30 PM. Please use the following teleconference information:

(b) (4)
Code: (b) (4)

Again, our apologies to the Division for having to push this TC to Friday of a holiday weekend.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Wednesday, May 25, 2011 10:18 AM
To: Burdette, Linda {PDR4~Nutley}
Subject: RE: NDA 202429 vemurafenib t-con proposed time- Friday May 27, 3:30pm?

Alright – thank you.

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Wednesday, May 25, 2011 10:08 AM
To: Ferrara, Theresa
Subject: Re: NDA 202429 vemurafenib t-con proposed time- Friday May 27, 3:30pm?

Let me check. Will get back to you as soon as I hear back from them.

Sent using BlackBerry

From: Ferrara, Theresa <Theresa.Ferrara@fda.hhs.gov>
To: Burdette, Linda {PDR4~Nutley}
Sent: Wed May 25 10:06:54 2011
Subject: NDA 202429 vemurafenib t-con proposed time- Friday May 27, 3:30pm?

Hi Linda,

Would the Roche team be available on Friday, May 27th 3:30pm for brief tele-conference?

I did leave a voicemail on your work number suggesting this new date/time, but you can disregard. Please let me know if this is an option.

Thank you.

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
05/25/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Tuesday, May 24, 2011 4:48 PM
To: 'Burdette, Linda'
Cc: Kacuba, Alice; Berkhin, Maria {PDR4~Nutley}
Subject: NDA 202429 vemurafenib, clinical & stats information requests

Dear Linda,
Please refer to your NDA 202429, vemurafenib. The review team has the following information requests, which are listed below. Please provide us a response as soon as possible, or before Wednesday, June 1st. Thank you.

Clinical:

Please submit the internal pathology review of any de novo melanomas in patients who have been treated with vemurafenib.

Statistics:

Please submit

- 1) SAS programs to derive dataset EFEX;
- 2) SAS programs to create Figure 14.2/10, including not only those for the table of subgroup results, but also those for the plot itself.

Please let me know if there are any questions or concerns.

Best regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
05/24/2011

Ferrara, Theresa

From: Fourie Zirkelbach, Jeanne
Sent: Monday, May 23, 2011 3:46 PM
To: 'linda.burdette@roche.com'
Cc: Ferrara, Theresa; Liu, Qi (CDER)
Subject: NDA 202429 vemurafenib (BRAF inhibitor) IR from Clinical Pharmacology reviewer

Dear Linda,

Regarding NDA 202-429:

Could you please provide rationale for selection of the

(b) (4)

Could you please submit this information as soon as possible.

Thanks,
Jeanne

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/s/

THERESA A FERRARA
05/24/2011



NDA 202429

INFORMATION REQUEST

Hoffman-La Roche Inc.
Attention: Duane Voss
Program Director, Technical Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Voss:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vemurafenib (R05185426) 240 mg tablets.

We also refer to your 31 March 2011 submission, containing Chemistry, Manufacturing and Controls drug substance and drug product quality information.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response to all items by 1 June 2011 in order to continue our evaluation of your NDA.

1. Stability: Only three months of primary stability data on the commercial lots were submitted in the original application. In order to ensure a commercially viable expiration dating period, provide updated stability data for the commercial lots of drug substance and drug product (manufactured July – Sept 2010). Note that this request is case-specific and does not reflect any deviation from the Agency's expectation that all NDAs are complete at the time of initial submission.
2. Drug Product Expiry: Provide a timeline for the manufacture of your drug product, from first addition of excipient to the drug substance - including transport, hold and processing times. Include the actual timelines for the manufacture of the three commercial batches submitted.

3.



4. Composition Tables: Revise all composition tables in the submission to include the content of [REDACTED] (b) (4) [REDACTED] – for example Table 1 p.22 and Table 3 p.26 Section 2.3 Quality Overall Summary, etc.
5. Specifications: Revise the all specifications to identify the test method used (e.g. drug product specifications in section 3.2.S.4.1 and starting material specifications in section 3.2.S.2.3, etc.)
6. Starting Material Batch History: Provide a listing of the lots of starting materials used in the manufacture of the commercial and development batches of drug substance (e.g. Tables 1 and 2 in section 3.2.S.4.4). Provide Certificates of Analysis for the lots and test results from in-house testing.
7. The dissolution data provided in the application supports [REDACTED] (b) (4) [REDACTED].
8. Please explain the [REDACTED] (b) (4) [REDACTED].

If you have any questions, call Scott N. Goldie, Ph.D., Senior Regulatory Project Manager for Quality at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Sarah Pope Misinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment 1
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
05/20/2011

Ferrara, Theresa

From: Fourie Zirkelbach, Jeanne
Sent: Wednesday, May 18, 2011 4:42 PM
To: 'Linda.burdette@roche.com'
Cc: Liu, Qi (CDER); Ferrara, Theresa
Subject: NDA 202429 vemurafenib (BRAF inhibitor) IR from Clinical Pharmacology reviewer

Dear Linda,

Regarding NDA 202-429:

1. In section 12.3 of the annotated label, the PK of vemurafenib is reported as follows: "... (b) (4) ."

In the sentence just prior to the sentence above, you state that the PK parameters for vemurafenib were determined using NCA in a Phase 1 and Phase 3 study.

- It is not clear to the reviewer where these PK parameters reported in the label are from. Are they from the NCA using the Phase 1 and Phase 3 study data, or are they from the NP22676 trial? If they are from the NP22676 trial, could you please indicate why you chose to report the data from this trial and not those from the NP25163 trial?
- Could you please provide the dataset used in the NCA analysis that was used to obtain the PK parameters in the annotated label?

2. Could you please expand on your rationale for selection of the bid dosing regimen vs. a single daily dose regimen?

It would be appreciated if you could provide a response to these questions as soon as possible, or within 5 business days.

Thank you,
Jeanne

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/s/

THERESA A FERRARA
05/18/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Thursday, May 12, 2011 8:53 AM
To: 'Burdette, Linda'; Berkhin, Maria {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: RE: NDA 202429 (vemurafenib) acknowledgement letter

Hi Linda,

Yes – the letter lists the tradename “Zelboraf” as a placeholder. However, an official review by our colleagues in the OSE office is underway. Once they have an outcome about the proprietary name, you will receive notification.

Theresa

From: Burdette, Linda [mailto:linda.burdette@roche.com]
Sent: Wednesday, May 11, 2011 5:49 PM
To: Ferrara, Theresa; Berkhin, Maria {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: RE: NDA 202429 (vemurafenib) acknowledgement letter

Thanks Theresa.

I know we are going to have question from the team on the use of the tradename “Zelboraf” mentioned in your acknowledgment letter. We submitted a new proprietary name application to the NDA the day after we filed, and Zelboraf was our first priority. Is this tradename mentioned in your acknowledgment letter as a placeholder until we hear from OSE on their assessment of our tradename proposals?

I just want to be sure to manage the team’s expectations appropriately.

Thanks very much for your help on this.

Best Regards,
Linda

Linda Burdette, Ph.D.
Roche
PD Regulatory
973-235-4578 (phone)
973-562-3700 (FAX)

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From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Wednesday, May 11, 2011 4:56 PM
To: Burdette, Linda {PDR4~Nutley}; Berkhin, Maria {PDR4~Nutley}
Cc: Kacuba, Alice
Subject: NDA 202429 (vemurafenib) acknowledgement letter

Hi Linda and Maria,

Please find attached an electronic copy of the NDA acknowledgement letter for NDA 202429 (vemurafenib). You

will receive a hard copy through the mail. If you have any questions, feel free to call or email me.

Best regards,
Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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THERESA A FERRARA
05/12/2011



NDA 202429

NDA ACKNOWLEDGMENT

Hoffman-La Roche Inc.
Attention: Linda J. Burdette, Ph.D.
Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Burdette:

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: Zelboraf (vemurafenib) Tablet, 240 mg

Date of Application: April 27, 2011

Date of Receipt: April 28, 2011

Our Reference Number: NDA 202429

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 27, 2011, 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).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinformo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 202429** submitted on April 27, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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 Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call me, at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Theresa Ferrara, MPH
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

THERESA A FERRARA
05/10/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Monday, May 09, 2011 11:53 AM
To: 'Klimek, Matthew'
Subject: RE: Roche NDA 202,429 (Vemurafenib) Post-Submission Meeting - tentative date May 23, 2011
Attachments: FVDR form 10 2010.doc

Hi Matt,

Thank you for a quick reply.

You will come to Building 22 of the White Oak campus. Please plan to arrive by 10:15-10:20am, as it can take some time for everyone in the group to get a temporary badge and to go through security. If there are any attendees who are not US citizens, I will need the attached foreign visitor form completed and returned to me by the end of this week. Additionally, I would request that you send me the list of expected attendees at the same time of any foreign visitor forms.

On the day of the presentation, I will meet you in the lobby around 10:30am and we will proceed to the meeting conference room.

Thank you.

Theresa

From: Klimek, Matthew [mailto:matthew.klimek@roche.com]
Sent: Monday, May 09, 2011 8:56 AM
To: Ferrara, Theresa
Subject: RE: Roche NDA 202,429 (Vemurafenib) Post-Submission Meeting - tentative date May 23, 2011

Hi Theresa,

We accept the date, Monday, May 23rd 11am-12pm. I will provide a slide deck by Friday May 20th (1pm).

Please provide the location and any further information as its available. We are looking forward to meeting with you and the team!

Thanks,
Matt

From: Ferrara, Theresa [mailto:Theresa.Ferrara@fda.hhs.gov]
Sent: Friday, May 06, 2011 2:13 PM
To: Klimek, Matthew {PDR3~Nutley}
Subject: RE: Roche NDA 202,429 (Vemurafenib) Post-Submission Meeting - tentative date May 23, 2011
Importance: High

Dear Matt,

We have a tentative date scheduled for Monday, May 23rd, 11:00am – 12:00pm. Please confirm if this date is acceptable.

I can have your slides projected for you, however, you must send them to me by Friday, May 20th 1pm.

Alternatively, if you do not send the slides to me, you will be responsible for bringing your own projector to display slides.

Please be concise with your information, as there will only be 50 minutes for your presentation.
Please keep in mind if this date is not acceptable, another meeting would not be scheduled till later in the year.

Please reply as soon as possible.

Thank you.
Theresa

From: Klimek, Matthew [mailto:matthew.klimek@roche.com]
Sent: Friday, April 29, 2011 1:31 PM
To: Ferrara, Theresa
Subject: Roche NDA 202,429 (Vemurafenib) Post-Submission Meeting

Hi Theresa,

Regarding NDA 202,429 for Vemurafenib (completed April 27th), we'd like to know if the agency will be inviting Roche for a post-submission meeting? If the agency will be inviting us, can you let us know when we may expect an invitation or provide details regarding the meeting (ie timing, expectations)if available?

Thanks and have a good weekend,
Matt

Matthew Klimek, PharmD
Regulatory, Product Development
Hoffman La-Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199
Phone: (973) 235-7882
Mobile: (201) 310-7206
Fax: (973) 562-3700
Email: matthew.klimek@roche.com

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITIZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	May 23, 2011 10:45am
MEETING ENDING DATE AND TIME	May 23, 2011 12:00pm
PURPOSE OF MEETING	Sponsor presentation for NDA 202429
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22, Room 2205
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Theresa Ferrara, Regulatory Project Manager Office of Oncology Drug Products Division of Drug Oncology Products WO 22, Room 2317 301-796-2848
ESCORT INFORMATION (If different from Hosting Official)	

Please allow a minimum of ten (10) business days in submitting information for processing. Upon completion please email the form(s) to: OSO-FOREIGN VISIT (Global Address Book) For late notice visits and other questions please contact:

Sebastian Malvagna (301) 796-4606
Michael Haggerty (301) 796-4593
Steven Russell (301) 796-4604

Sebastian.Malvagna@fda.hhs.gov
Michael.Haggerty@fda.hhs.gov
Steven.Russell@fda.hhs.gov

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/s/

THERESA A FERRARA
05/10/2011

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/s/

THERESA A FERRARA
05/09/2011

Ferrara, Theresa

From: Ferrara, Theresa
Sent: Thursday, May 05, 2011 2:27 PM
To: 'Burdette, Linda'
Cc: Berkhin, Maria (PDR4~Nutley); Kacuba, Alice
Subject: NDA 202429 InfoRequest- sent 5.5.11

Dear Linda,

I have the following information request from the review team for Roche's NDA 202429:

Please submit the file "RunlogNM7.for" that was used in your population PK analysis. Please submit this ASAP; but no later than May 18, 2011 COB.

Thank you.

Theresa

Theresa Ferrara, MPH
Regulatory Project Manager
Division of Drug Oncology Products, CDER, FDA
email: Theresa.Ferrara@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A FERRARA
05/05/2011

REQUEST FOR CONSULTATION

TO (Office/Division): IRT group, Devi Kozeli

FROM (Name, Office/Division, and Phone Number of Requestor):
Theresa Ferrara, RPM 301-796-2848
Office of Oncology Drug Products/ DDOP

DATE
5/05/11

IND NO.

NDA NO.
202429

TYPE OF DOCUMENT
new NDA submission

DATE OF DOCUMENT
04/28/11

NAME OF DRUG
vemurafenib

PRIORITY CONSIDERATION
priority

CLASSIFICATION OF DRUG
Oncology

DESIRED COMPLETION DATE
request for expedited
review - May 31, 2011

NAME OF FIRM: Hoffman-La Roche, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

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| <input checked="" type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
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| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS: NDA 202429 submitted electronically. There is a dedicated QT substudy in the Phase 2 single arm trial that was submitted as part of the NDA. Of note, there appears to be a 12-15 ms prolongation of the QTc interval at the proposed therapeutic dose and simulations indicate potentially higher QTc prolongations in obese individuals.

Clinical: Yang-Min (Max) Ning, Amy McKee, and Geoff Kim
Clin Pharm: Jeanne Fourie Zirkelbach, Qi Liu, and Justin Earp

EDR Location: \\CDSesub1\EVSPROD\NDA202429\202429.enx

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

Theresa Ferrara	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

THERESA A FERRARA
05/05/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Theresa Ferrara, RPM 301-796-2848 Office of Oncology Drug Products, Division of Drug Oncology Products	
REQUEST DATE April 29, 2011	IND NO.	NDA/BLA NO. 202429	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Vemurafenib (proprietary name, Zelboraf, submitted to OSE 4.28.11)	PRIORITY CONSIDERATION Yes – Priority, expedited review	CLASSIFICATION OF DRUG Oncology	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) Tentatively September 16, 2011; however, timelines will be discussed during upcoming planning meeting
NAME OF FIRM: Hoffman-La Roche, Inc		PDUFA Date: (priority) October 28, 2011	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
EDR link to submission: EDR Location: \\CDSESUB1\EVSPROD\NDA202429\202429.enx			
Sending consult in today because this application will be a priority expedited review. Please let me know who the reviewer will be so that I can invite them to all meetings. Planning meeting to discuss timelines will be forthcoming after review assignment is given. Thank you.			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: [TBD] Labeling Meetings: [TBD] Wrap-Up Meeting: [TBD]			
SIGNATURE OF REQUESTER			

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL/ DARRTS <input type="checkbox"/> HAND

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/s/

THERESA A FERRARA
04/29/2011

REQUEST FOR CONSULTATION

TO (Office/Division): **CDER OPS IO Environmental Assessment**

FROM (Name, Office/Division, and Phone Number of Requestor): **Scott N. Goldie, OPS/ONDQA/6-2055**

DATE
14 April 2001

IND NO.

NDA NO.
202429

TYPE OF DOCUMENT
Original Submission

DATE OF DOCUMENT
31 March 2011

NAME OF DRUG
vemurafenib

PRIORITY CONSIDERATION
**TBD - Accelerated
Priority likely**

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
ASAP

NAME OF FIRM: **Hoffman-La Roche Inc**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
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| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
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| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
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| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Enviromental Assessment requested on NME drug. Presubmission of quality module with clinical (final) module expected in May 2011. Increased survivability of unresectable stage IIIc or stage IV BRAF mutation positive melanoma of new oncology drug. High probability of priority review - may be accelerated review timeline as well. eCTD application.

SIGNATURE OF REQUESTOR
Scott N. Goldie

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SCOTT N GOLDIE
04/14/2011

HARIPADA SARKER
04/19/2011

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Friday, January 21, 2011
Meeting Location: FDA White Oak, Bldg 22, Room 1309

Application Number: IND 073620
Product Name: RO5185426 (PLX 4032)
Indication: for the treatment of patients with melanoma positive for BRAF^{v600} mutation by the cobras[®] 4800 BRAF V600 Mutation test (b) (4)

Sponsor/Applicant Name: Hoffman-La Roche
Meeting Request Date: September 17, 2010
Meeting BGP date: December 17, 2010

Meeting Chair: John Johnson, M.D., Clinical Team Leader
Meeting Recorder: Theresa Ferrara, Regulatory Project Manager

FDA ATTENDEES

Richard Pazdur, M.D., Director, OODP
Robert Justice, M.D., M.S., Director, DDOP
Amna Ibrahim M.D., Deputy Director, DDOP
Anthony Murgo, M.D., Deputy Director, DDOP
Max Ning, M.D., Medical Officer, DDOP
John Johnson, M.D., Clinical Team Leader, DDOP
Ke Liu, M.D., Clinical Team Leader, DDOP
Marc Theoret, M.D., Medical Officer, DBOP
Sarah Pope Miksinski, Ph.D., Branch Chief, ONDQA, Division I, Branch II
Haripada Sarker, Ph.D., CMC Lead, Branch 2/ DNDQA I/ONDQA
Sue-Ching Lin, M.S., R.Ph., CMC Reviewer, ONDQA, Division I, Branch II
Pengfei Song, Ph.D., Clinical Pharmacology Reviewer
Kelly Flipski, Ph.D., Clinical Pharmacology Reviewer
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Reviewer
Rajeshwari Sridhara, Ph.D., Division Director, DB 5
Shenghui Tang, Ph.D., Team Leader, DB 5
Qiang (Casey) Xu, Ph.D., Mathematical Statistician, DB 5
Donna Roscoe, CDRH
Maria Chan, CDRH
Robert Young, M.D., DSI
Jeanne Perla, DRISK
Alice Kacuba, RN, MSN, RAC, Chief, Project Management Staff
Susan Jenney, M.S., Safety Regulatory Project Manager

SPONSOR ATTENDEES

Hoffman-La Roche, Inc.

Cynthia Dinella, Pharm.D, Vice President, US Regulatory Affairs
Lisa Luther, Senior Director, US Regulatory Affairs
Krishnan Viswanadhan, Pharm.D., Oncology Group Director, Regulatory Affairs
Linda Burdette, Ph.D., Global Regulatory Leader
Cheryl Elder, Pharm.D., US Regulatory Partner
Flavia Borellini, Ph.D., Project Leader
Richard Lee, M.D., Development Sub-Team Leader
Jacob Zeffren, M.D., Safety Science Leader
Joe Grippo, Ph.D., Clinical Pharmacology
Betty Nelson, Ph.D., Biostatistics Team Leader
Somnath Sarkar, Ph.D., Deputy Global Head Oncology Biostatistics
Lauren Merendino, US Brand Director
Andrew Joe, Clinical Science
Jeannie Hou, Clinical Science

Roche Molecular Systems

Lesley Farrington, Regulatory Affairs
Suzanne Cheng, Ph.D., Genomics and Oncology

Plexxikon

Keith Nolop, M.D., Chief Medical Officer

1.0 BACKGROUND

RO5185426 (PLX 4032) is a highly selective inhibitor of BRAF^{V600E} mutation and has been under co-development by Roche and Plexxikon, Inc. Both Phase 1 and Phase 2 clinical studies have shown that the product is highly active in patients with advanced melanoma positive for the specific mutation who have received prior systemic therapy. A randomized, open-label Phase 3 trial of the product comparing with DTIC for both OS and PFS is being conducted in patients with the BRAF mutation who have not been previously treated with systemic therapy. A planned interim analysis of the two endpoints of the Phase 3 trial would be performed as pre-specified in the recently revised SAP. Depending on whether the interim analysis generates positive results or not, the sponsor proposed two different NDA submission scenarios to seek advice from the Agency in support of marketing approval of the product for the treatment of advanced melanoma positive for the mutation. The meeting focused on addressing the sponsor's questions and providing reasonable answers and/or solutions toward a successful NDA submission and efficient evaluation of the submission. See the Meeting Minutes for details.

2.0 DISCUSSION

Question 1

Scenario 1: Phase 3 Filing with Positive Progression Free Survival (PFS) and Overall Survival (OS) at the Interim Analysis (IA)

- (a) Does the Agency agree that the proposed NDA package would support a NDA filing for full approval?

FDA Response to Question 1a:

Yes. Positive results from the final PFS and interim OS analysis conducted as pre-specified in the recently revised SAP for the Phase 3 trial would likely support an NDA filing to seek full approval.

Meeting discussion: The FDA is amenable to reviewing an application for accelerated approval consisting of the phase 1 and phase 2 data (based on overall response rate).

- (b) Does the Agency agree that the totality of the data provides sufficient preclinical and clinical experience to support an indication inclusive of “*patients with unresectable Stage IIIc or Stage IV melanoma*”?

FDA Response to Question 1b:

The precise indication will be a review issue.

- (c) In order to provide the physician with data supporting use of RO5185426 across the populations included in the proposed indication, Roche proposes that in addition to providing data supporting PFS and OS improvement in the Phase 3 study, the study design and key efficacy data (e.g., BORR and response duration) from the Phase 2 Study (NP22657) in previously treated patients be included in the label. Does the Agency agree?

FDA Response to Question 1c:

This will be a review issue.

- (d) Roche intends to provide a safety update approximately 3 months after NDA submission. Does the Agency agree with the above proposed content and timing for the safety update?

FDA Response to Question 1d:

The proposal for the 3 month safety update is acceptable.

Meeting Discussion: Sponsor proposes to submit updated median OS and RR analysis with the 3 month safety update. The OS analysis will reflect crossover of patients. FDA agrees. Phase 3 safety data will not be pooled with phase 1 and phase 2.

Question 2

Scenario 2: Filing Strategy with DSMB Recommendation to Continue the Phase 3 Study without Release of Results

- (a) Does the Agency agree that a filing based on BORR in the single arm Phase 2 Study (NP22657) supported by data from PLX06-02, would qualify for accelerated approval under 21 CFR §314.500, Subpart H, provided that the results of the Phase 3 Study (NO25026) in previously untreated patients with Stage IIIc or Stage IV melanoma is provided as a post-marketing commitment?

FDA's response to Question 2a:
The plan is acceptable.

- (b) Roche proposes to provide the final results of Study NO25026 as a post-approval commitment in order to convert the application to full approval. Does the Agency agree that submission of the Phase 3 supplement with clinically meaningful benefit in PFS, regardless of the OS result, is sufficient to convert the application to full approval?

FDA's response to Question 2b:
This will be a review determination. A clinically meaningful improvement in the PFS may be associated with a clinically meaningful benefit to support conversion to full approval if the overall risk-benefit profile is favorable in the Phase 3 trial. The OS result must be submitted whether favorable or not.

- (c) In the case where the DSMB recommends crossover at the IA based on compelling PFS results and a strong OS trend, the final analysis for OS from the Phase 3 Study (NO25026) which will be provided as confirmatory data is likely to be confounded by crossover:
- (i) What are the Agency's thoughts on describing the results of the OS IA in the label?

FDA's response to Question 2c (i):
Labeling is a review issue.

- (ii) Would the Agency consider an OS claim based on comparison to historical control data in patients treated with dacarbazine?

FDA's response to Question 2c (ii):
No.

INDICATION FOR V600 MUTATION

Question 3

BRAF protein activation occurs with any of the known perturbation of the protein structure at amino acid 600. The most common mutation occurs when valine is replaced with glutamic acid (V600E). A number of rarer mutations have been reported. Among melanomas, these include other replacement amino acids such as lysine (V600K), aspartic acid (V600D), arginine (V600R). Although the cobas[®] 4800 BRAF V600 Mutation Test was designed to detect the predominant V600E mutation, the test does display some cross-reactivity with other rarer mutations affecting codon 600.

(b) (4)

(b) (4)

FDA Response to Question 3:

No. The indication will be limited to those described in the eligibility criteria of your trial.

Meeting Discussion: The precise indication will be a review issue.

SAFETY DATABASE

Question 4

The safety analyses intended for submission in the NDA will be derived from a Roche quality-checked database containing all data for the studies, as of their individual clinical data cut-offs, that are to be included for each filing scenario. Does the Agency consider the totality of safety data in patients treated with RO5185426 sufficient to characterize the safety profile of RO5185426 for each filing scenario?

FDA Response to Question 4:

Yes.

ADVERSE EVENTS OF INTEREST

Question 5

- (a) Based on the safety data presented, does the Agency agree with the proposed analyses of cuSCC and/or other adverse events of interest?

FDA Response to Question 5a:

The proposed analyses appear reasonable. Please make sure that the proposed preferred terms for cuSCC are able to identify all patients diagnosed with cuSCC during and after the study. All cuSCC diagnosed should be clearly documented in CRFs.

- (b) Based on the QTc data presented (see Section 6.7 and Appendix 4), does the Agency agree with the proposed analyses for QTc prolongation as described below?

FDA Response to Question 5b:

Your proposed analyses appear acceptable. The QT-IRT would like to review the final study report for ECG sub-study NP22657 when submitted. Since RO5185426 is a QT prolonger based on your preliminary analysis, we recommend the following in your ongoing clinical studies:

- **Monitoring Safety ECGs at baseline, following the first dose, at steady state and periodically thereafter**
- **Monitoring electrolytes periodically**
- **Excluding subjects with congenital long-QT syndrome**
- **Specifying criteria for dose-modification and discontinuation in patients with post-treatment QTc > 500 ms.**

Meeting Discussion: Sponsor acknowledges the Agency's recommendation and will amend all ongoing clinical trials accordingly.

ROLLING SUBMISSION

Question 6

- (a) Does the Agency agree with the proposed schedule for submission?

Scenario 1 (Submission based on Phase 3 IA Filing)

January Module 4, Module 2.4 and Module 2.6

March Module 3
May Modules 1 and 5, plus remainder of Module 2
Request for Priority Review

FDA Response to Question 6a:
Acceptable.

Scenario 2 (Submission based on Phase 2 AA Filing)
January Module 4, Module 2.4 and Module 2.6
March Modules 1, 2, 3 and 5
Request for Priority Review

(b) Does the Agency have any recommendations that would facilitate review of the rolling submission?

FDA Response to Question 6b:

Please submit information listed in the following table as early as possible

Investigator Name, Address, Telephone #	# Enrolled	# Responders	# Serious Adverse Events	# Protocol Violations

Meeting Discussion: The sponsor proposed to submit the information above on the phase 2 and phase 3 studies, as currently planned.

ADDITIONAL LABELING QUESTIONS

Question 7

Attempts to identify the effect of food intake on the pharmacokinetics of RO5185426 within the Phase 1 Study (PLX06-02) resulted in too few evaluable patients to provide unequivocal interpretation of these data. To identify the effect of food on RO5185426 exposure, a single-dose two-way crossover (fasted, high fat meal) study, NP25396, will be initiated in December 2010 (S-245, submitted September 2, 2010). Data from this study will not be available for the anticipated filing in 2Q2011. Based on the Agency's feedback to the protocol for the Expanded Access Program (ML25597), Roche proposes (b) (4)

Does the Agency agree this is a reasonable approach based on the currently available data?

FDA Response to Question 7:

Your proposed approach appears acceptable.

Question 8

To address the risk of SCC, a Risk Management Plan (RMP) to monitor, evaluate and treat events of SCC has been implemented in all RO5185426 trials. As per the RMP, lesions suspicious for cuSCC are to be excised and sent for centralized dermatopathology review.

Roche proposes that the label include SCC results based on the clinical database (including potential risk factors, time to onset, etc) and the central dermatopathology classification of excised lesions (e.g., see Section Table 8). Additionally, Roche proposes that the label should inform the physician as to the nature of these lesions, time of onset, the general appearance, and potential risk factors for development of cuSCC.

Does the Agency agree with inclusion in the label of these data and the instructions listed below for monitoring and managing cuSCC?

FDA Response to Question 8:

The information for labeling about the risk of cuSCC appears adequate with the current understanding of this risk. The FDA may have additional labeling recommendations after the data is submitted and reviewed.

Meeting Discussion: FDA suggested that sponsor investigate in relation to the use of BRAF inhibitor in preclinical models to explore possible differences between cuSCC and non cuSCC.

Question 9

Roche plans to submit a Medication Guide in the NDA describing the signs and symptoms of clinically significant adverse events, including cuSCC, photosensitivity, abnormal liver function, QT prolongation, and drug-drug interactions and providing instructions to patients on what to do in the event they experience the adverse events.

Will inclusion of a Medication Guide trigger a Risk Evaluation and Mitigation Strategy?

FDA Response to Questions 9:

With the passage and implementation of FDAAA, FDA reviews and approves Risk Evaluation and Mitigation Strategy (REMS), not Risk Management Plans.

You propose to submit a Medication Guide. In addition, you outline "education and outreach" materials and activities consistent with a Communication Plan to address the risk of SCC. Any proposal including a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use described under 505-1(e) of FDAAA should be submitted as a proposed Risk Evaluation and Mitigation Strategy (REMS). At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a 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. We will determine the need for a REMS during the review of your application.

If you plan to submit a REMS with the original NDA submission, please submit all planned materials (e.g., proposed Medication Guide, proposed communication and education materials) identified within the plan that will be necessary to implement your proposal. We remind you that

- **Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.**
- **Product marketing materials generally are not appropriate to educate about product risks**

Meeting Discussion: At this time, sponsor acknowledges focusing on the risk of cuSCC per use of a Medication Guide.

RISK MANAGEMENT AND PHARMACOVIGILANCE PLANS

Question 10

With the understanding that final assessment will depend on the review of all data, and provision of a detailed plan in the NDA, does the Agency agree with the general provisions of the Risk Management Plan outlined below?

FDA Response to Question 10:

This is a review issue. Please see the response to question 9.

Question 11

In addition to routine pharmacovigilance procedures, which will include a dedicated report on SCC appended to the Annual Safety Report, Roche proposes to implement the use of a guided questionnaire to obtain SCC information from health care professionals. One year post-implementation, Roche proposes to perform an evaluation of the utility of the questionnaire. This evaluation will be utilized to decide whether continued use of the questionnaire is warranted.

Does the Agency agree with the proposed Pharmacovigilance Plan?

FDA Response to Question 11:

This is a review issue. Please see the response to question 9.

POST-FILING

Question 12

What are the Agency's expectations for the review process, interactions with the sponsor, and timing of milestone activities?

FDA Response to Question 12:

Please refer to the following website for 21st century review timelines.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf>

Question 13

Based on the data presented in the Briefing Package and with the understanding that this will be dependent on review of all data provided in the NDA, what post-marketing commitments might the Agency foresee?

FDA Response to Question 13:

This will be a review issue.

Question 14

Does the Agency anticipate an Advisory Committee for this NDA? If yes, can the Agency comment on the following:

- (a) What does the Agency already foresee as potential topics for discussion at an Advisory Committee?

FDA Response to Question 14a:

This is a review issue.

- (b) At what point during the NDA review can the sponsor expect to be notified about timing of the Advisory Committee meeting?

FDA Response to Question 14b:

You will be notified once the review identifies potential ODAC issues.

Additional Comments:

Attached are two documents from the Division of Scientific Investigation (DSI) that will assist in your NDA submission. This will not be discussed at the meeting. Please direct all questions to DSI.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

Sponsor provided handout during meeting to discuss the proposed timeline for submission of the NDA.

Minutes Preparer:

{See appended electronic signature page}

Theresa Ferrara
Regulatory Project Manager

Attachment(s)
Sponsor handout (Timeline)

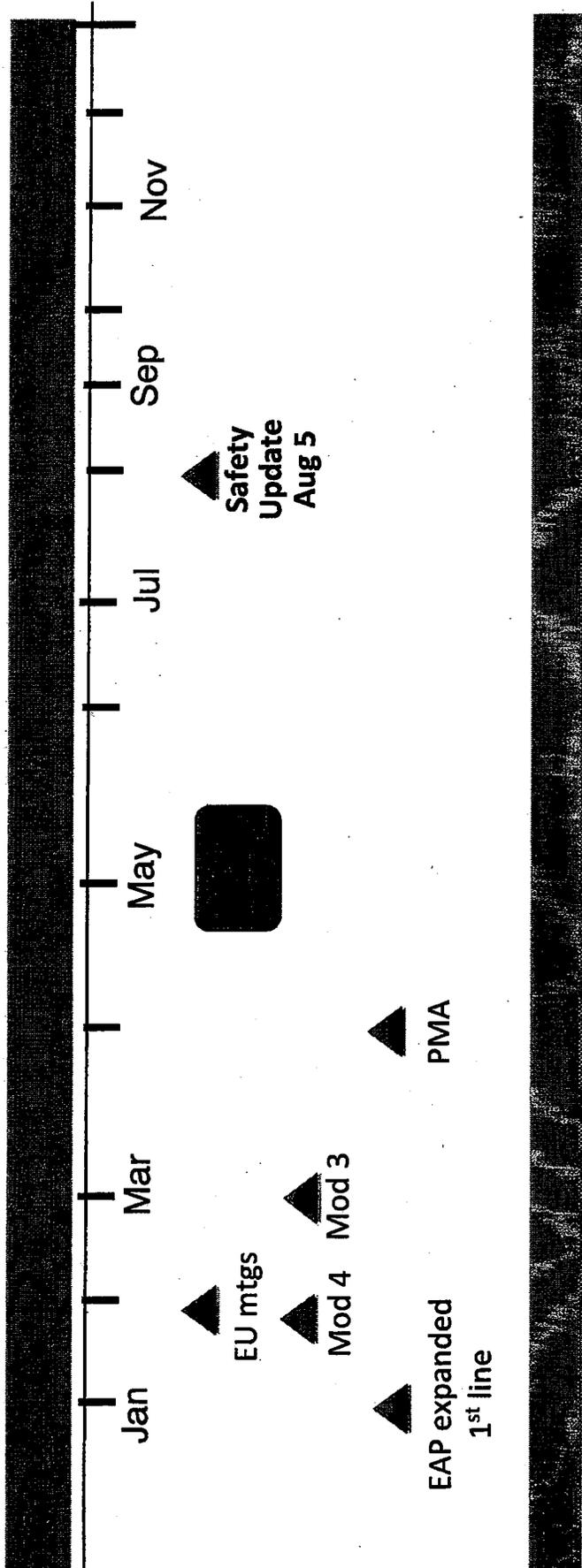
Meeting Chair

{See appended electronic signature page}

John Johnson, M.D.
Clinical Team Leader



Timeline for NDA and Safety Update (SU)



Cutoff for NDA
 Sep 27, 2010

Cutoff for SU
 Jan 31, 2010

DB lock for NDA
 Oct 27, 2010

DB lock for SU
 Mar 11, 2010

Cutoff
 Dec 30th

DB lock for NDA
 Feb 7

Cutoff
 Apr 1

DB lock for SU
 May 15

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/s/

JOHN R JOHNSON
02/10/2011

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA, Chemistry, Manufacturing and Controls
Meeting Date and Time: Friday, December 03, 2010, 1100 – 1200 ET
Meeting Location: Teleconference
Application Number: IND 73620
Product Name: R05185426 (PLX4032)
Indication: Treatment of advanced cancer
Sponsor/Applicant Name: Hoffman-La Roche, Inc.
Meeting Chair: Richard T. Lostritto, Ph.D.
Meeting Recorder: Scott N. Goldie, Ph.D.

FDA ATTENDEES

Angelica Dorantes, Ph.D.	ONDQA Biopharmaceutics Team Leader (<i>via telephone</i>)
Scott N. Goldie, Ph.D.	Senior Regulatory Health Project Manager for Quality
Sue Ching Lin, Ph.D.	Quality Reviewer
Richard T. Lostritto, Ph.D.	Division Director
Sarah Pope Miksinski, Ph.D.	Branch Chief
Haripada Sarker, Ph.D.	CMC Team Leader

SPONSOR ATTENDEES

Linda Burdette, Ph.D.	Global Regulatory Leader
Walfrido Antuch Garcia, Ph.D.	Technical Regulatory Affairs
Markus Deichmann, Ph.D.	Analytical Development
Rina Gamboni, Ph.D.	Technical Regulatory Affairs
Peter Leutolf, Ph.D.	Pharmaceutical Development
Hans-Juergen Mair, Ph.D.	Analytical Development
Anni Pabst-Ravot, Ph.D.	Analytical Development
Linda Rubia,	Technical Team Leader
Fabian Schwarb, Ph.D.	Technical Regulatory Affairs
Richard Steinbach,	Technical Regulatory Affairs
Hung Tian, Ph.D.	Analytical Development
Duane Voss,	Technical Regulatory Affairs

1.0 BACKGROUND

RO5185426 (originally designated as PLX4032) is currently under codevelopment by Hoffmann-La Roche Inc. (Roche) and Plexxikon Inc. for the treatment of metastatic melanoma and other advanced cancers in patients with tumors positive for the BRAF mutation. The purpose of this Type B meeting is to discuss with the Agency the Roche proposal for a stability strategy that would support a possible early submission of Module 3. This stability strategy would mitigate the effect an early submission will have on the amount of drug product stability data that will be available at the time of NDA submission. Roche also requests discussion on additional questions regarding the MBP.

Meeting Chronology: Meeting requested 24 September 2010 (SD-290); Meeting granted 18 October 2010; Briefing package submitted 03 November 2010. (SD-335); Preliminary responses sent 02 December 2010; Teleconference with altered agenda held as scheduled on 03 December 2010.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls (CMC)

Briefing Package Question 1: Does FDA accept Roche's proposed finished product primary stability filing strategy to support a potential early submission of Module 3?

FDA Response to Question 1: As per the Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMPs), all NDAs are to be complete in the original submission. Less than twelve months of long-term stability data in the original submission of an NDA is normally considered to be incomplete and thus is a fileability issue. However, in this specific case, your approach is acceptable as an exception, provided that the overall (supportive and primary) stability data package submitted in the initial NDA submission is sufficiently representative of the proposed commercial manufacturing product and process.

While your proposal to submit a stability update is acceptable in this specific case, updates (as CMC amendments to the filed NDA) should **only** include updated stability data for previously-submitted batches manufactured via the previously-submitted process and packaged in the same container closure(s). Further, for stability data provided during the review clock, use the exact same format for presentation as in the original submission such that the updated stability data is clearly visible as an extension of the data set of each particular batch being updated. Note that any additional CMC information submitted in stability updates may result in a clock extension.

As part of the initial NDA, provide a comprehensive risk assessment which adequately links the stability data from Roche Basel to that generated by the proposed commercial manufacturing process and site. Co-precipitated solids of this type tend to be hygroscopic and may exhibit poor physical stability (i.e., reversion accelerated by moisture). In your risk assessment, address the physical stability of the co-precipitate (e.g., with respect to solubility and dissolution) and its relationship to humidity and temperature. This risk assessment will need to support filing with less than the usual twelve month minimum stability data package for the registration batches.

Discussion: Hoffman-La Roche acknowledged receipt of FDA's response. Hoffman-La Roche stated that they plan to submit their CMC module by the end of March, 2011 and expect to submit the recommended stability data as described in the preliminary responses. FDA recommended that any stability updates be submitted prior to the starting of the review clock. The meeting participants discussed the scope and location of the risk assessment, and concluded that the risk assessment would be best submitted in a single section with appropriate references to that section in the NDA.

Briefing Package Question 2a: Does FDA agree with Roche's proposal to assign a retest date to the drug substance co-precipitate (MBP)?

FDA Response to Question 2a: Your general approach is reasonable. However, assign an expiration dating period to the co-precipitate (MBP) instead of a retest date.

Discussion: Hoffman-La Roche acknowledged receipt of FDA's response and clarified that the expiration dating period of MBP [REDACTED] (b) (4) FDA accepted this proposal.

Briefing Package Question 2b: Does the FDA agree that for the purpose of assigning an expiration date to a batch of film-coated tablets, that it may be calculated from the initial date on which the manufacture [REDACTED] (b) (4) occurs at the Roche Segrate, Italy facility?

FDA Response to Question 2b: Your approach is reasonable. Provide your detailed justification in the NDA when submitted.

Discussion: Hoffman-La Roche acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Briefing Package Question 3: To comply with requirements set forth in 21 CFR 314.50(d)(1)(ii)(c) regarding the submission of the proposed or actual master production records, Roche intends to include a copy of the proposed drug product Master Production Batch Record (unexecuted) in the NDA. Executed batch records of the primary and commercial site stability batches included in the NDA will be available at their respective manufacturing sites and will be available upon inspection. Does FDA agree with this approach?

FDA Response to Question 3: No. In accordance with 21 CFR 314.50(d)(1)(ii)(b), include in your NDA the executed batch records for representative batches used in clinical and primary stability studies.

Discussion: Hoffman-La Roche acknowledged receipt of FDA's response. FDA and Hoffman-La Roche agreed that executed batch records of two of the three batches produced in Basel and used in the clinical trials and as primary stability batches with three executed batch records from Segrate and one unexecuted master batch record from the proposed commercial site would be sufficient to include with the NDA submission.

Briefing Package Question 4: Please refer to Roche's July 2, 2010 submission containing format questions for the NDA, and to the responses received on September 10, 2010. Question 6, regarding Module 3, and FDA's response was as follows:

(a) The NDA will be submitted electronically using the eCTD format. Does the requirement to submit three copies of a Method Validation Package composed of copies of documents taken from CMC volumes exist under eCTD?

(b) If so, would one electronic copy be sufficient, or should this information be submitted separately on three individual disks?

FDA Response to Question 4: You are not required to submit three copies of a method validation package. Include the method validation package as a series of links to appropriate leaf files in the CTD NDA submission under Section 3.2.R., Regional Information. Duplicates of existing files should not be submitted.

Discussion: Hoffman-La Roche acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Additional CMC comments:

1. Revise your specifications for the drug substance, MBP, and drug product in accordance with ICH Q3A and ICHQ3B. The specifications should include the following acceptance criteria for organic impurities: each specified identified impurity, each specified unidentified impurity, any unspecified impurity with an acceptance criterion of not more than the identification threshold, and total impurities. Provide chemical names and structures for the impurities that exceed identification thresholds. Provide appropriate acceptance criteria for particle size distribution in both the drug substance and MBP.

Discussion: Hoffman-La Roche acknowledged receipt of FDA's response and committed to update the specifications and acceptance criteria in accordance with the manufacturing data and FDA's recommendations. Hoffman-La Roche committed to include when appropriate, justification for their specifications and acceptance criteria.

2.2. ONDQA Biopharmaceutics Comments:

Comment: The following ONDQA Biopharmaceutics Comments were read into the record during the meeting as they were not available to be included with the preliminary responses. Hoffman-La Roche acknowledged receipt of FDA's comments. FDA provided for further written communications as necessary to clarify these points.

1. We noticed in Appendix 5 - "Specifications for Drug Product" of your meeting's document, that the proposed specification for the dissolution test is (b) (4)



- The dissolution profile data from the bio- and primary stability batches should be used for the setting of the dissolution specification of your product (i.e., specification-sampling time point and specification value).
 - The in vitro dissolution profiles should encompass the timeframe over which at least (b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.
 - For an immediate release product the selection of the specification time point should be where $Q =$ (b) (4) dissolution occurs.
2. Also, please include in your NDA submission the dissolution method development report supporting the selection of the proposed test. The dissolution report should include the following information;
 - solubility data for the drug substance covering the pH range,
 - detailed description of the dissolution method proposed for 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/identify the proposed dissolution method as the most appropriate. The testing conditions used for each test should be clearly specified,
 - 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), and
 - include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the validation data for the dissolution method and analytical method.

Discussion: Hoffman-La Roche requested that they receive a written copy of the ONDQA Biopharmaceutics Comments that were read into the record during the meeting as soon as possible. FDA recommended that the dissolution development report contain all data used to propose the dissolution specification and the results of the dissolution method development.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no outstanding issues that require further discussion at the conclusion of the teleconference.

4.0 ACTION ITEMS

FDA committed to provide a written copy of the ONDQA Biopharmaceutics comments and to further written correspondence regarding the ONDQA Biopharmaceutics comments if necessary.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Sr. Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

{See appended electronic signature page}

Richard T. Lostritto, Ph.D.
Director
Division of New Drug Quality Assessment 1
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments, handouts or slides distributed for the teleconference.

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

/s/

SCOTT N GOLDIE
12/18/2010

RICHARD T LOSTRITTO
01/03/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 73, 620

MEETING MINUTES

Hoffmann-La Roche Inc.
Attention: Ms. Duane Voss
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110

Dear Ms. Voss:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PLX4032 (R05185426).

We also refer to the teleconference between representatives of your firm and the FDA on July 17, 2009. The purpose of the meeting was to gain the Agency's feedback on the company's proposals related to the designation of drug substance and starting materials, formulation bridging, and drug product stability plans at the time of NDA.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Deborah Mesmer, Regulatory Project Manager at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Deborah M. Mesmer, M.S.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and
Manufacturing Science
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
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Hoffman-La Roche (Roche)
Application Number:	IND 73,620
Product Name:	RO5185426
Teleconference Requestor:	Ms. Duane Voss, Program Director, Drug Regulatory Affairs, Roche
Teleconference Type:	Chemistry, Manufacturing & Controls (CMC) End of Phase 2 (EOP2)
Teleconference Category:	Type B
Teleconference Date and Time:	Friday, July 17, 2009, 11:00 – 12:00 ET
Received Briefing Package	June 12, 2009
Teleconference Chair:	Sarah Pope Miksinski, Ph.D.
Teleconference Recorder:	Deborah Mesmer, M.S.

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment (ONDQA)

Patrick J Marroum, Ph.D., Biopharmaceutics
Deborah Mesmer, M.S., Regulatory Health Project Manager-Quality
Sarah Pope Miksinski, Ph.D., Branch Chief
Anne Marie Russell, Ph.D. Review Chemist
Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead

Division of Drug Oncology Products (DDOP)

Pengfei Song, Ph.D., Pharmacologist

EXTERNAL ATTENDEES:

ROCHE

Duk-Soon Choi, PhD, Analytical Development
Joe Grippo, PhD, Clinical Pharmacologist
Raman Iyer, PhD, Pharmaceutical Development
Hans-Juergen Mair, PhD, Chemistry Team Leader
Colm O'Mahony, PhD, Technical Regulatory Affairs
Anni Pabst-Ravot, PhD, Analytical Development
Markus Deichmann, PhD, Analytical Development
Linda Rubia, Technical Team Leader
Kathleen Schostack, PhD, Project Leader
Fabian Schwarb, PhD, Technical Regulatory Affairs
Navnit Shah, PhD, Pharmaceutical Development
Hung Tian, PhD, Analytical Development
Duane Voss, Regulatory Affairs

1.0 BACKGROUND

RO5185426 (originally designated PLX4032) is currently under co-development by Hoffmann-La Roche Inc (Roche) and Plexxikon Inc for the treatment of metastatic melanoma and other advanced cancers in patients with tumors positive for the BRAF V600E mutation. Roche is currently conducting an extended Phase I study. Roche met with FDA for an EOP2 meeting on May 15, 2009, to discuss the clinical and non-clinical development plans to support registration of RO5185426 for treatment of metastatic melanoma.

Roche submitted a Type B, End-of Phase 2, CMC meeting request dated May 6, 2009, to the Division of Drug Oncology Products, received on May 7, 2009. The meeting request was transferred to ONDQA, and a meeting was granted on May 20, 2009, for a teleconference meeting to be held on July 17, 2009. The meeting briefing package dated June 11, 2009, was received on June 12, 2009. The preliminary responses to the questions contained in the meeting briefing package were archived and shared with Roche on July 16, 2009, to promote efficient discussion at the meeting. The teleconference was held as scheduled on July 17, 2009.

2.0 DISCUSSION**2.1.1 Question 1**

(b) (4)

FDA Response to Question 1: There is insufficient information in your meeting package to consider this question. Additionally, the intent of your proposal is unclear. Clarify the rationale behind your proposal. Provide a detailed description of the interaction between the polymer and the API in the complex.

Teleconference Discussion: Roche and FDA held a detailed discussion describing the interaction between the polymer and the API to evaluate the current proposal to designate

the co-precipitated non-crystalline API-polymer complex (RO5185426-006) as the drug substance. FDA requested that Roche provide additional information in a submission to the IND and request written feedback to specific questions contained in the submission. FDA recommended that Roche include a reference to the CMC EOP2 meeting and send an electronic courtesy copy to the Quality Project Manager (D. Mesmer) to facilitate the review. The submission should include the rationale for this designation and a description of the interaction between the polymer and the API. Only new information needs to be submitted—a cross reference to the meeting briefing package (and the data contained therein) is sufficient. Alternatively, another meeting request could be sent further along in the development process.

2.1.2 **Question 2:** Does the FDA agree that [REDACTED] (b) (4) [REDACTED] may be classified as starting materials for the planned registration/commercial synthesis of RO5185426-006?

FDA Response to Question 2: No. FDA does not consider [REDACTED] (b) (4) [REDACTED] an acceptable starting material. FDA recommends that you propose starting materials used earlier in the synthesis of the drug substance.

Include the following information in the NDA for any proposed starting materials. This information will be reviewed for adequacy during the NDA review.

- Complete impurity profiles
- In-house acceptance criteria and Vendors' Certificates of Analysis
- Brief descriptions of the synthetic strategies and methods used for manufacture
- Detailed discussions regarding any impurities found in the starting materials, which may be carried forward into the drug substance
- Proposed controls and analytical methods that are suitable to separate and measure the appropriate impurities
- Complete supplier information
- Data from purging studies performed using potential impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to the desired levels in the drug substance
- Change control strategies for any potential revisions to the manufacture of proposed starting materials, including the mechanism for vendor reporting of any manufacturing changes made for any proposed starting material
- Supportive literature data if available
- Validated analytical methods such as HPLC to assess the chemical and chiral purity of the starting materials.
- Analytical methodology used for the drug substance that 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.

- Highly purified and well characterized reference starting materials and data confirming the stability of the starting materials.

Additionally, note that the classification of [REDACTED] (b) (4) as a starting material will also depend on the outcome of Question 1.

Teleconference Discussion: Roche acknowledged receipt of FDA's preliminary response and requested clarification regarding the information necessary to support the designation of starting materials. FDA clarified that the bulleted list is not a listing of new requirements, but a starting point for the review of supporting materials that are typically needed to evaluate the choice of starting material during the review of the application. This list was shared by FDA to avoid the need for an information request letter early in the review cycle. FDA emphasized that the proposed starting material has sufficient similarity to the core moiety of the drug substance that it does not meet the criteria for a starting material. FDA recommended that Roche consider a starting material earlier in the synthesis. Roche then proposed a starting material from earlier in their synthetic pathway, specifically in step (b) (4). FDA recommended that Roche include sufficient scientific justification, with the provided list as a starting point, to support their choice of starting materials. FDA stated that the choice of starting materials is a review issue to be evaluated during the review of the application.

- 2.1.3 **Question 3:** Does the FDA agree that the formulations used during the Phase 1 study and supported by the additional planned clinical pharmacokinetic (PK) study are adequately bridged?

FDA Response to Question 3: Based on our preliminary review of your meeting package, your approach appears generally acceptable. However, the final determination will be a review issue.

Teleconference Discussion: Roche acknowledged receipt of FDA's preliminary response. No further discussion occurred at the meeting.

- 2.1.4 **Question 4:** Does the FDA agree that three months stability data for the registration batches produced at the commercial facility may be submitted as an amendment during NDA review?

FDA Response to Question 4:

- a. No. As per *Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMP)*, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a commercially viable expiry. Any information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Teleconference Discussion: Roche acknowledged receipt of FDA's preliminary response. Roche asked for clarification regarding the submission of supportive stability data during the review period. FDA stated that the application must have sufficient data at the time of filing, as insufficient stability data to establish a commercially viable expiry is a potential reason for refusing to file the application.

- b. Include in the original NDA submission sufficient primary stability data on registration batches to support a commercially viable expiry. Stability data on batches produced at manufacturing sites other than the facility producing the registration batches would be considered secondary and supportive.

Teleconference Discussion: Roche acknowledged receipt of FDA's preliminary response. FDA clarified that the data to support the commercially viable expiry should be based on the sites of commercial manufacturing to support the determination of expiry for the drug product.

Additional comments:

Clarify the dosage strengths in terms of API (RO5185426) and API-polymer complex (RO5185426-006) for all formulations. For example, the amount of API in the unit dose is not clear in Table 2 and Table 3.

Teleconference Discussion: Roche acknowledged receipt of and agreed with FDA's preliminary response. No further discussion occurred at the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no other issues currently requiring discussion.

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 CONCURRENCE:

{See appended electronic signature page}

Deborah Mesmer, M.S.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73620	GI-1	HOFFMANN LA ROCHE INC	PLX4032

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

/s/

DEBORAH M MESMER
10/15/2009

Sarah Pope Miksinski
10/15/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073620

MEETING MINUTES

Hoffman-La Roche Inc.
Attention: Duane Voss
Program Director, Technical Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Voss:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO5185426 (PLX4032).

We also refer to the teleconference between representatives of your firm and the FDA on Friday, December 3, 2010. The purpose of the meeting was to discuss your proposed data package to support the submission of module 3 of your NDA and the amount of drug product stability data available at the time of NDA submission.

A copy of the official minutes of the teleconference is attached 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) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Sr. Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

MEETING DATE: May 15, 2009

TIME: 4:00 PM - 5:00 PM

LOCATION: CR 1315

IND: 73620

Meeting Request Submission Date: March 13, 2009

FDA Response Date: March 24, 2009

Briefing Document Submission Date: April 15, 2009

Additional Submission Dates: May 5, 2009

DRUG: PLX4032; RO5185426

SPONSOR/APPLICANT: Hoffman-La Roche, Inc.

TYPE of MEETING:

1. Type B End of Phase 2 meeting to discuss the clinical and non-clinical development plans, as well as the co-development program for an *in vitro* diagnostic test to support the registration of PLX4032 in the treatment of patients with metastatic melanoma that is positive for the BRAF V600E mutation.
2. Proposed Indication: The treatment of V600E-positive metastatic melanoma.

FDA PARTICIPANTS:

Robert Justice, M.D., Division Director

Anthony Murgo, M.D., Acting Deputy Director

Virginia E. Maher, M.D., Clinical Team Leader

Yang-Min Ning, M.D., Clinical Reviewer

Albert Deisseroth, M.D., Clinical Reviewer

Robert Kane, M.D. Clinical Reviewer

Haleh Saber, Ph.D., Pharmacology Team Leader

Qi Liu, Ph.D., Acting Clinical Pharmacology Team Leader

Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer

Robert Becker, M.D., CDRH Team Leader

Gene Pennello, Ph.D., CDRH Statistician

Lakshmi Vishnuvajjala, Ph.D. Branch Chief, Diagnostics Branch, Division of Biostatistics, Office of Surveillance and Biometrics, CDRH

Donna Roscoe, Ph.D., Biologist

Shenghui Tang, Ph.D., Acting Biostatistics Team Leader

Somesh Chattopadhyay, Ph.D., Biostatistics Reviewer

INDUSTRY PARTICIPANTS:

Roche

Cindy Dinella, PharmD, Regulatory Affairs

Lisa Luther, Regulatory Affairs

Jennifer Dudinak, PharmD, Regulatory Affairs

Linda Burdette, PhD, Regulatory Affairs

Kathleen Schostack, Project Leader

Catherine Wheeler, MD, Oncology

Richard Lee, MD, Clinical Scientist

Peter Bridge, MD, Drug Safety

Joe Grippo, PhD, Clinical Pharmacologist

Kisook Yoo, PhD, Biostatistician

Hysun Oh, PhD, Toxicology

Jeff Sosman, Professor of Medicine, Vanderbilt University

Roche Diagnostics

Karen Long, Regulatory Affairs, Vice President

Suzanne Cheng, PhD, Genomics and Oncology

Jeff Lawrence, MD, Genomics and Oncology Clinical Affairs

Plexikon

Keith Nolop, MD, Chief Medical Officer

Gideon Bollag, PhD, Head of Discovery

BACKGROUND: Type B End of Phase 2 meeting request dated March 13, 2009, (S-0043) SDN 51 was received March 16, 2009 from Hoffman-La Roche Inc. The meeting was granted March 24, 2009 with a meeting date of May 15, 2009 which was confirmed by email. The meeting preparation package, dated April 15, 2009 (S-0049) SDN 57 was received April 16, 2009. The purpose of this meeting according to the sponsor is to discuss the clinical and non-clinical development plans, as well as the co-development program for an *in vitro* diagnostic test to support the registration of PLX4032 in the treatment of patients with metastatic melanoma that is positive for the BRAF V600E mutation.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question 1

During the dose escalation phase of PLX06-02, efficacy signals, including substantial and confirmed tumor regressions and stable disease for up to 14 months of treatment, have been reported in patients with tumors positive for activating BRAF mutations, the target of

RO5185426. Conversely, patients with WT V600 BRAF have shown disease progression consistent with timelines reported in the literature, suggesting differential responsiveness to RO5185426 treatment. As the majority of the patients enrolled in the dose escalation phase of PLX06-02 have metastatic melanoma, these preliminary efficacy signals are supportive of continued evaluation of the clinical activity of RO5185426 in this patient population.

Dose-limiting toxicities of Grade 3 fatigue, rash and arthralgia have defined the maximum tolerated dose (MTD). Based on related adverse events of photosensitivity and cutaneous squamous cell carcinoma (SCC), patients in these studies are instructed to limit exposure to the sun and ultraviolet rays and to report any new, changing or enlarging skin growth to their doctors. A dermatologic consult at baseline and at regular intervals is included as part of the risk management plan in the extension cohorts of the Phase 1 study and all subsequent clinical studies. Based on information available at this time, the potential benefits of treatment of metastatic melanoma with RO5185426 are considered to outweigh potential risks of SCC because of the high unmet medical need in this patient population, the substantial tumor regressions observed with RO5185426 treatment, and the ability to monitor and treat cutaneous SCC.

(a) Does the Agency agree that the efficacy and safety observed to date support initiation of an uncontrolled single arm study in previously treated patients and a controlled randomized study in previously untreated V600E-positive patients with metastatic melanoma?

FDA Response:

- **Please see responses to questions 2&3**
- **Additional studies should only be initiated under carefully controlled conditions, including adequate informed consent.**
- **A Data Safety Monitoring Board should be formed to monitor your international safety database.**
- **We agree, in part, with your plan to monitor patients closely for the development of squamous cell carcinomas. Please continue to follow patients for at least 6 months after the last dose of study drug. Please plan to examine patients for the development of squamous cell carcinomas in locations other than the skin (careful head and neck examination, chest CT).**

Discussion: The sponsor will follow all patients until death. The sponsor is examining the mechanism of action for the development of squamous cell carcinoma. The sponsor will initiate a comprehensive long term plan for monitoring the safety of the study agent. This plan would permit the initiation of further clinical studies.

(b) Are the safety monitoring and risk management plans in the ongoing extension cohorts of the Phase 1 study considered acceptable for the proposed uncontrolled and randomized studies?

FDA Response: See response to Question 1a. Please present a safety update following completion of the extension cohorts in your current study.

Discussion: The sponsor will submit a safety update after twenty patients in the melanoma extension cohort have received thirty days of study drug.

Question 2

Roche and Plexxikon are currently planning to conduct two studies to support accelerated approval of RO5185426 for the treatment of patients with V600E-positive metastatic melanoma. The first study is a single arm uncontrolled trial of RO5185426 in previously treated patients with V600E-positive metastatic melanoma (n=80). The second study is a randomized, double-blind, controlled trial in previously untreated patients with V600E-positive metastatic melanoma, with the objective of demonstrating the superiority of RO5185426 to dacarbazine in PFS (based on 85 events in about 110 randomized patients) to support accelerated approval, and in overall survival (based on 500 events in about 760 randomized patients) to support full approval. The studies will be initiated approximately in parallel. As the uncontrolled single arm study would provide earlier results in previously treated patients, we are considering two potential scenarios that could enable accelerated approval.

Scenario A - NDA filing based on the single arm uncontrolled study: In this scenario, a substantial improvement of $\geq 30\%$ in overall response rate (ORR) with RO5185426 to that reported in the literature in previously treated patients with V600E-positive metastatic melanoma would serve as the basis for accelerated approval based on the high unmet medical need in this population. Duration of response will be provided as key secondary efficacy information. The randomized study would be ongoing at the time of filing and would provide supporting progression-free survival (PFS) and overall survival (OS) data at later time points.

If the uncontrolled single arm study demonstrates an overall response rate of $\geq 30\%$ (estimated 95% confidence intervals of 20%, 41%) as assessed by a blinded independent centralized review (BICR), with an acceptable safety profile in this patient population, would the Division consider this study as the basis for accelerated approval?

FDA Response: No.

- **Studies have not shown marked and consistent response rates in melanoma. Therefore, no relationship has been established between an endpoint such as response rate and an endpoint which demonstrates clear clinical benefit such as overall survival.**
- **The safety issues associated with your product are best addressed in a randomized study.**

Discussion: FDA recommended that the sponsor conduct a randomized Phase 3 trial. The sponsor asked if a single arm trial would be acceptable for accelerated approval. After discussion of the FDA's concerns with this proposal, FDA stated that we would be willing to discuss this again once the sponsor has data suggesting impressive activity.

Question 3

Scenario B – NDA filing based on the surrogate endpoint of PFS in the randomized controlled study.

In the second scenario, accelerated approval would be based on the demonstration of 100% improvement in median PFS with RO5185426 compared to dacarbazine (HR = 0.5, 4 months vs. 2 months, respectively) in a randomized, double-blind, controlled trial in previously untreated patients with V600E-positive metastatic melanoma. Statistical significance of the treatment difference will be tested at the alpha level of 0.025 (2-sided) considering a single randomized study for registration. The PFS analysis will be done when 85 events are observed. Assuming a total of approximately 110 patients (including about 10% ITT non-evaluables) would need to be randomized to have the required number of PFS events, approximately 5 months would be required for enrollment and approximately 7 months for follow-up.

The study will be powered for both PFS (analysis at filing) and OS (confirmatory analysis post-filing for full approval), using an overall Type I error rate of 0.025 (2-sided). This study would be continuing at the time of NDA submission (based on PFS analysis) to obtain mature OS results. One interim analysis of OS is planned when 50% of the target number of events (250 out of 500 deaths) are observed. A total of about 760 patients who are positive for the V600E mutation will be enrolled in a 2:1 randomization ratio for RO5185426 (+ placebo) vs. dacarbazine (+ placebo) to observe 500 death events for the final analysis.

The OS results will be submitted when the interim analysis results show statistical significance or when the final analysis is done (i.e., in case the interim analysis results are not significant) to provide confirmatory evidence of the clinical benefit of RO5185426 for the surrogate endpoint of PFS.

All safety data, and the results of the interim OS analysis, will be reviewed by a Data Safety Monitoring Board (DSMB), which will consist of physicians with expertise in metastatic melanoma and at least one statistician, all of whom are external and independent of the Sponsors and project team. The DSMB will initially review partially unblinded data (at the treatment group level) and will have the option to unblind the data completely (at the patient level), if needed. Based on the results of the interim OS analysis, the DSMB may recommend either to continue the study without changes or to terminate the trial based on the demonstration of a significant OS advantage of RO5185426 compared to dacarbazine. In the event the DSMB recommends to continue the trial, details of the data reviewed will not be communicated to the Sponsors to minimize potential bias in the remaining study conduct.

- (a) **Given the unmet medical need in metastatic melanoma, does the Agency agree that the overall design of the single randomized controlled study, with strong evidence of efficacy in the primary endpoint of PFS, is sufficient to support accelerated approval of RO5185426 for the proposed indication of the treatment of patients with V600E-positive metastatic melanoma?**

FDA Response: No.

- **There is no established relationship between progression free survival and overall survival in this condition. We recommend that you modify your randomized study so that overall survival is the primary endpoint.**

Discussion: FDA stated that PFS is not an adequate surrogate endpoint in metastatic melanoma.

- (b) **Could the Division comment specifically on the following design elements of the randomized controlled study:**
- **Comparator, blinding, no crossover upon disease progression**
 - **Patient population (V600E-positive patients) and inclusion/exclusion criteria**
 - **Starting dose and dose modification scheme**
 - **Primary and secondary endpoints**
 - **Blinded independent centralized review of scans and data safety monitoring board**
 - **General statistical considerations, including the timing of PFS/OS analyses and the overall Type I error rate of 0.025 (2-sided)**

FDA Response:

- **Please provide references to support the dose and schedule of dacarbazine you have chosen.**
- **We are concerned that patients and investigators may be unblinded by the development of adverse reactions to study drug or DTIC. Please provide references concerning the incidence of photosensitivity with dacarbazine.**
- **We agree with your plan to conduct a double-blind trial and to avoid patient crossover.**
- **We do not agree with your plan to enter patients with Stage IIIc disease. Given the potential risks associated with your study drug, it should not be used in the adjuvant setting until more is known about these risks.**
- **Please see our comments below concerning patient age and the presence of the V600E mutation. Please see additional comments.**

- **We cannot comment on your starting dose until we have reviewed the adverse event profile from all 20 patients in the 960 mg cohort in your extension study. Please present data concerning the adverse event profile in the 960 mg cohort.**
- **Your dose modification scheme appears acceptable. However, we cannot comment prior to review of the impact of dose modifications on your Phase 1-2 study. Please present data concerning the ability of your dose modification scheme to mitigate subsequent adverse events.**
- **Please see our comment above concerning your primary endpoint.**
- **Your plan for blinded radiological review appears to be acceptable.**
- **Please see the response above concerning your Data Safety Monitoring Board.**
- **The randomization is said to be stratified only when separate randomization is applied within each combination of the stratification factors. If a minimization algorithm is used to balance randomization across different factors, the randomization should not be called a stratified randomization. You should not use a stratified analysis unless you stratify using the same factors at randomization. Even when the same stratification factors used at randomization are used to perform a stratified analysis, the number of patients for each combination of the stratification factors has to be sufficiently large for the results to be interpretable.**
- **To claim efficacy based on secondary endpoints after the primary endpoint has shown efficacy, the type I error rate must be adjusted for multiple secondary endpoints.**
- **For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive and clinically meaningful efficacy findings so that a second trial would be ethically or practically impossible to perform.**

Discussion: The sponsor will present evidence that truly unresectable Stage IIIc patients have a natural history similar to Stage IV patients. The sponsor will propose a plan to ensure that Stage IIIc patients entered on this study are truly unresectable.

Question 4

Based on evidence that RO5185426 selectively targets tumors with the V600E mutation, the clinical development plan is designed to evaluate the efficacy and safety of RO5185426 V600E-positive patients, with WT V600 patients (n=19-35) to be explored in a cohort of the uncontrolled study described in Question 2. The WT V600 status will be confirmed by sequencing to ensure the required number of patients with the correct WT V600 status.

Would the Agency support this approach for the evaluation of patients with WT V600 metastatic melanoma, and specifically comment on the cohort size, clinical endpoint of overall response rate, and the futility criterion of overall response rate <15% to demonstrate the lack of RO5185426 activity in these patients?

FDA Response: No.

- **It is unclear whether patients with WT Raf will benefit from study drug. More information about the safety profile of this agent will help determine whether WT Raf patients should be selected and treated as you propose.**
- **If the risks associated with the use of RO5185426 can be managed, we agree that the response rate of patients with WT V600 should be determined.**
- **Treatment of WT V600 patients, if undertaken, should be in the context of the intended use population for an approvable drug claim. Testing of WT V600 patients will be most informative if done in a different trial (i.e., a trial suitably designed for possible drug approval).**
- **WT V600 patients are not the complement of patients identified as “positive” by your test, since patients with V600K and perhaps V600R or V600D are split between “positive” and “negative” results. To assess the likelihood of response (or other endpoint) in marker negative patients, treatment of test “negative” patients is preferred over treatment of patients who are explicitly WT V600.**
- **Since the relationship between response rate and clinical benefit has not been established in melanoma, we cannot comment on your futility criterion (response rate < 15%).**
- **Studying efficacy and safety in WT V600 patients as well as in V600E positive patients would be important for evaluating the clinical effectiveness of the biomarker test. Therefore this component of the uncontrolled study is valuable to CDRH when evaluating the test.**

Discussion: The sponsor indicated that there is no intent to treat WT patients as part of the current study plans. This will limit the claims that can be made for the device, which remains a Class 3 device for use as a companion diagnostic.

Question 5

The clinical pharmacology development program to support registration of RO5185426 will include the following assessments in patients with V600E-positive metastatic melanoma. All of the clinical pharmacology studies will be performed with the proposed market formulation, 240 mg film-coated (MBP) tablets:

- ***QTc Evaluation.*** Rigorous QT/QTc assessments with matching pharmacokinetic assessments will be made in all patients in the uncontrolled trial in lieu of conducting a separate dedicated QTc study.
- ***Food Effect.*** The effect of food on RO5185426 exposure will be examined by steady-state crossover in V600E-positive patients in the fasted or fed states.
- ***Drug-Drug Interactions.*** The potential for RO5185426 to elicit drug-drug interactions (CYP450-dependent metabolism) will first be evaluated in V600E-positive patients using a cocktail approach. Patients will be administered a combination of 5 probe compounds simultaneously. Based on these data, additional studies designed to further evaluate the effect of RO5185426 on specific CYP450s may be conducted. In addition, the effect of RO5185426 on transporter-mediated mechanisms may be examined.
- ***Pharmacokinetic (PK)/pharmacodynamic (PD) Relationship.*** A PK/PD study will be conducted in V600E-positive patients to evaluate the PK characteristics of RO5185426 across a range of doses for labeling purposes. Paired biopsies (baseline, Day 15) will be used to evaluate PK/PD relationships for the BRAF pathway in these patients.
- ***Mass Balance.*** A mass balance study will be conducted in V600E-positive patients.
- ***Special Populations.*** At this time, no studies are planned with RO5185426 in special populations (e.g., patients with hepatic or renal impairment).

Could the Agency comment on the clinical pharmacology program, specifically:

- (a) Does the Agency agree that the overall clinical pharmacology program would support registration of RO5185426?

FDA Response: The overall clinical pharmacology program appears acceptable. We remind you that the results from the mass balance study will determine the need for organ dysfunction studies (renal and/or hepatic).

Discussion: None.

- (b) Does the Agency agree that the ECG monitoring/pharmacokinetic sampling plans in the uncontrolled study (N=99-115) to assess QT/QTc is sufficient for registration and that a separate study is not required?

FDA Response: Your proposed QT assessment is acceptable to detect large effects on the QTc interval. In the absence of both positive and negative controls, your QT assessment will not be able to detect small effects (< 10 ms).

In addition to the proposed central tendency analysis of ECG parameters, we also recommend that you perform the following analyses:

1) Categorical analysis: number and percentage of individuals with:

- a.) Absolute QT/QTc values > 450 ms, >480 ms, and >500 ms; as well as the number and percentage of individuals with change from baseline > 30 ms and > 60 ms.
- b.) PR changes from baseline = 50% if absolute baseline value was < 200 ms and = 25% if absolute baseline value was > 200 ms.
- c.) QRS changes from baseline = 50% if absolute baseline value was < 100 ms and = 25% if absolute baseline value was > 100 ms.

2) Number and percentage of individuals with abnormal ECG findings.

3) Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or arrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.

4) Assessment of the relationship between RO5185426 concentrations and changes in the baseline-adjusted QTc interval.

Discussion: FDA recommended that additional questions about the QTc interval be directed to the Project Manager (James Saunders).

- (c) Does the Agency agree that the proposed PK/PD study across relevant doses with the to-be-marketed formulation would be sufficient to characterize the pharmacokinetic profile of RO5185426 in the label?

FDA Response: This appears reasonable; however, the final determination will be a review issue.

Discussion: None.

Question 6

The NDA will include all available safety data at the time of filing from the uncontrolled metastatic melanoma study, the randomized controlled metastatic melanoma study, the Phase 1 study, the Phase 1 metastatic melanoma extension cohort, and clinical pharmacology studies. Depending on early availability of sufficient efficacy data, a safety database of approximately 400 patients treated with RO5185426 is anticipated at the time of filing for accelerated approval. Additionally, safety data from approximately 20 patients with metastatic colorectal cancer in the

extension cohort of the ongoing study, PLX06-02, and potentially additional patients in a planned uncontrolled study in patients with refractory metastatic colorectal cancer would be available.

Would the Agency consider this safety database as sufficient to support accelerated approval of RO5185426 for the proposed indication?

FDA Response: We cannot comment on the adequacy of the safety database prior to review of the adverse event profile of your study drug. We recommend that you submit the full report of the current Phase I study after completion.

Discussion: None.

Question 7

The clinical studies for registration are currently designed to use the BRAF companion *in vitro* diagnostic (IVD) test to identify V600E-positive patients for inclusion into these trials.

(a) Does the Agency agree with the focus on the V600E mutation which is the predominant activating BRAF mutation?

FDA Response: It is reasonable that the drug be evaluated in patients whose mutation status is V600E positive since the most common BRAF mutation is the V600E mutation.

Discussion: None.

(b) Does the Agency anticipate that the BRAF companion IVD test would be indicated in the label for patient selection?

FDA Response: Yes. However, in the absence of an adequate evaluation in a marker negative population, the device intended use is limited (i.e., the device cannot be given a “predictive” claim in the labeling).

Discussion: None.

(c) Does the Agency agree that a coordinated review with CDRH is warranted to support accelerated approval of both RO5185426 and the BRAF IVD test?

FDA Response: Yes. Analytical validity of the device should be established before it is applied to samples from the trials. To decrease the business risks associated with co-development, you might consider establishing analytical validity for the device through a modular PMA, for which the analytical module is “accepted”, before using the device

to accrue pivotal trial patients. The data needed to establish clinical validity would follow in the final module of the PMA. Such an approach is contingent on having sufficient time available for modular PMA review. For more information refer to “Guidance for Industry and FDA Staff Premarket Approval Application Modular Review” available at <http://www.fda.gov/cdrh/MDUFMA/guidance/835.pdf>. Alternatively, analytical validity might be established through submission of the analytical data as part of a complete PMA.

Discussion: None.

- (d) Does the Agency agree that the companion diagnostic could be approved based primarily on analytical performance, in conjunction with the results of the uncontrolled trial with the cohort in WT patients?

FDA Response: No. Clinical effectiveness of the device should be based on data from the controlled, randomized trial. The analytical validity of the device used to select patients for your trial is the necessary foundation. Your proposal to demonstrate the analytical performance of the test by comparing both the V600E mutant and wild type samples from the uncontrolled trial to 454 sequencing will demonstrate the accuracy of the TaqMan method. If the risks associated with the use of RO5185426 can be managed, we recommend that patients with WT V600 should also be studied for response rate, OS, and PFS.

Please note, that 454 sequencing is not an FDA-cleared or approved method, nor is it considered a reference method (at this time only bi-directional sequencing with acceptable Phred scores is considered as a reference method). While 454 sequencing will likely be one suitable comparator, we have not yet resolved the accuracy requirements including discordant results. The accuracy will need to be demonstrated at your claimed limit of detection (5%).

The clinical performance of your test is linked to the performance of the drug. However, your study design, in which only “marker positive” patients will be accrued to the pivotal trial, carries implications for the claims that might be approved ultimately for both the device and the drug:

- In the absence of an adequate evaluation in a marker negative population, the device intended use will be limited (i.e., a “predictive” claim cannot be included in labeling).
- If the test must be modified to a version different from what was used to accrue patients to the trial, then depending on the nature of the changes made to the test, the clinical performance of the test and drug combination might be inconclusive. In the absence of a suitable concordance study (e.g., demonstrate that the modified device would have segregated the patients similarly using at least 95% of the specimens deemed marker positive and marker negative in the

trial) the status of drug efficacy in the subset of patients defined by the modified test may be indeterminable.

Discussion: Further discussions between the sponsor, CDRH, and CDER will be aimed at formalizing the analytical study plan, and the success criteria attached to it. A modular PMA submission plan may help to avoid problems from test evolution during the pivotal trial.

Question 8

- (a) Based on the low incidence of metastatic melanoma in children and the need first to establish the efficacy and safety of RO5185426 in adult patients, does the Agency agree with the plan to request a waiver in children less than 16 years of age?

FDA Response: We agree with your plans to request a pediatric waiver.

Discussion: None.

- (b) Does the Agency agree with the proposal to allow enrollment of patients 16 to 18 years of age into the randomized clinical trial and that this would provide sufficient data of the efficacy and safety of RO5185426 in a pediatric population?

FDA Response: No. Given the uncharacterized risks associated with your study drug, minors should not receive this agent until more is known about its risk profile and the management of this risk.

Discussion: None.

Question 9

The nonclinical toxicology program of RO5185426 was carried out in accordance with international regulatory guidances, i.e., the ICH M3 '*Guidance On Nonclinical Safety Studies For The Conduct of Human Clinical Trials And Marketing Authorization For Pharmaceuticals*' and S1A '*Guideline On The Need For Carcinogenicity Studies Of Pharmaceuticals*'.

A complete nonclinical program will be available at the time of filing to support the registration of RO5185426. The following toxicology studies have been completed to date:

- Single-dose toxicology studies in rats and dogs
- Repeat-dose toxicology and toxicokinetic studies in rats (2-week, 4-week, and 26-week) and dogs (4-week and 13-week)
- Safety pharmacology core battery studies (cardiovascular, CNS, respiratory functions)
- Genetic toxicology core battery assays (*in vitro* Ames and human chromosomal aberration, *in vivo* MNT)
- Embryo-fetal development toxicology studies in rats and rabbits (Segment II)
- *In vitro* phototoxicity study (murine 3T3 fibroblast neutral red uptake assay)

RO5185426 at doses up to the maximum feasible dose in the given formulation was well tolerated, and there were no significant drug-related adverse findings in any of the single-dose or repeat-dose toxicology studies for up to 26 weeks (rat) or 13 weeks (dog). In all of these studies, the NOAELs were the highest dose levels examined and the maximum feasible dose in the corn oil or MBP formulation. No safety signals were observed in the safety pharmacology core battery studies. There were no signs of genotoxicity in a standard core battery of tests. RO5185426 revealed no evidence of teratogenicity in rat or rabbit embryo/fetuses at doses up to the highest dose levels tested. Maternal toxicities (decreased food consumption and body weight gain) were observed in rats treated with 800 mg/kg/day and in rabbits treated with 450 mg/kg/day. RO5185426 was shown to be phototoxic based on the results of the *in vitro* test.

An *in vivo* 7-day phototoxicity study in hairless rats is currently ongoing.

The following toxicology studies are planned to be initiated in 2009 and full data for these studies will be provided in the NDA:

- A 9-month repeat-dose GLP toxicology and toxicokinetic study in dogs
- A fertility and early embryonic development toxicology study in rats (Segment I)
- A peri- and post-natal development toxicology study, including maternal function in rats (Segment III)

(a) Does the Agency agree that the above described non-clinical program is sufficient to support the registration of RO5185426?

FDA Response: Yes. However, acceptance of the data and adequacy of each study will be a review issue. For additional information, please see the ICH S9 DRAFT Guidance “Nonclinical Evaluation for Anticancer Pharmaceuticals,” currently under discussion, posted at <http://www.fda.gov/cder/guidance/8681dft.pdf>.

To better understand the safety profile of your drug, we strongly encourage you to study the mechanism of SCC development in patients e.g., whether this event is secondary to light exposure.

(b) Does the Agency agree with the plan not to conduct carcinogenicity studies with RO5185426 for the proposed indication of metastatic melanoma?

FDA Response: Yes.

Additional Comments:

- 1. Your entry criteria concerning prior radiation therapy in Study N025026 are unclear. It appears as if radiation therapy may be administered to the thorax within 2 weeks of entry. Please clarify.**
- 2. Please justify your plans to include patients with a QTc of 450 to 500 msec.**

- 3. You indicate that all of the patients enrolled in the WT cohort (initial sample size 19) will be confirmed WT V600 by sequencing methodology to ensure the required number of patients with the correct WT V600 status. The current test used to segregate marker BRAF V600E mutation positives from WT V600E patients (marker negatives) is intended to be the test used to exclude candidates from therapy. Therefore the WT cohort should only include the patients deemed negative by the TaqMan test (sequencing should be conducted after the trial is complete). Samples that were WT with the COBAS TaqMan test but V600E mutant by sequencing (and subsequently excluded from the trial) represent potential false negatives of the test. Keep a record of all discordant results. Indicate how much of the BRAF gene will be sequenced (the V600E snp or other alleles as well).**
- 4. For the phase 3 trial, patients should be selected on the basis of the TaqMan test alone. A second sequencing test should not be used to enrich the population, only to confirm results at the conclusion of the trial.**
- 5. You indicate that the TaqMan test detected 5/8 samples with the V600K and a V600D mutation bearing cell line (V600R inconclusive). It is likely these patients will be included in the trial. (Page 6). Are these mutations activating mutations and predicted to be responder phenotypes similar to the V600E mutation?**
- 6. The IDE report has not changed from the original IDE submitted In July 2007. Please refer to the original approval letter for additional requests for analytical performance. In addition, be prepared to demonstrate that melanin does not interfere with the assay or affect the selected cut-offs. Melanin extraction steps will need to be included as part of the final approved device.**
- 7. We recommend that you archive all samples for patients screened, including screened negative subjects who were not enrolled in the trial.**

James M. Saunders

Project Manager

Concurrence Chair: V. Ellen Maher ,M.D.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 73620

HOFFMANN LA ROCHE
INC

PLX4032

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/s/

VIRGINIA E MAHER
06/01/2009