

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203388Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED UPON AND  
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation or  
Composition) and/or Method of Use*

NDA NUMBER

203388

NAME OF APPLICANT/NDA HOLDER

Genentech, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME

ERIVEDGE

ACTIVE INGREDIENT(S)

Vismodegib

STRENGTH(S)

150 mg

DOSAGE FORM

Capsule

APPROVAL DATE OF NDA OR SUPPLEMENT

30 Jan 2012

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

**For hand-written or typewriter versions of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

7,888,364

b. Issue Date of Patent

15 Feb 2011

c. Expiration Date of Patent

11 Nov 2028

d. Name of Patent Owner

Genentech, Inc.  
Curis, Inc.

Address (of Patent Owner)

Genentech Inc., 1 DNA Way

City/State

South San Francisco, CA

ZIP Code

94080-4990

FAX Number (if available)

650-225-6000

Telephone Number

650-225-1000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<p><b>FDA will not list the patent in the Orange Book as claiming the drug substance if:</b></p> <ul style="list-style-type: none"> <li>• the answers to 2.1 and 2.2 are "No," or,</li> <li>• the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,</li> <li>• the answer to 2.3 is "Yes" and there is no response to 2.4, or,</li> <li>• the answer to 2.5 or 2.6 is "Yes."</li> <li>• the answer to 2.7 is "No."</li> </ul>		

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<p><b>FDA will not list the patent in the Orange Book as claiming the drug product if:</b></p> <ul style="list-style-type: none"> <li>• the answer to question 3.1 is "No," or,</li> <li>• the answer to question 3.2 is "Yes," or,</li> <li>• the answer to question 3.3 is "No."</li> </ul>		

**4. Method of Use**

**Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more approved methods of using the approved drug product?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product?	
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.)	

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.

Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

**5. No Relevant Patents**

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

*Michelle Kelen*

*2/24/12*

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Genentech, Inc.

Address

1 DNA Way

City/State

South San Francisco, CA

ZIP Code

94080-4990

Telephone Number

650-225-1000

FAX Number (if available)

650-225-6000

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
 Food and Drug Administration  
 Office of Chief Information Officer  
 1350 Piccard Drive, Room 400  
 Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## INFORMATION AND INSTRUCTIONS FOR FORM 3542

### PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.
- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

#### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

#### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

#### 4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

- 4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the approved drug labeling that is claimed by the patent.
- 4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

#### 5. No Relevant Patents

Complete this section only if applicable.

#### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 203388

SUPPL #

HFD # 107

Trade Name Erivedge

Generic Name vismodegib

Applicant Name Genentech, Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(1)

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

Applicant referred to CFR 314.108 (b)(2) in exclusivity 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:

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Name of person completing form: Mona Patel  
Title: Regulatory Project Manager  
Date: 1/25/2012

Name of Office/Division Director signing form: Patricia A. Keegan  
Title: Division Director

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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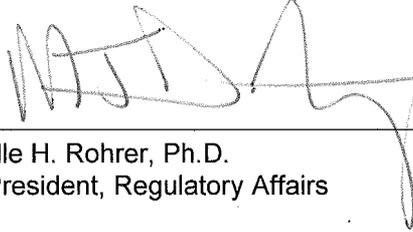
MONA G PATEL  
01/25/2012

PATRICIA KEEGAN  
01/26/2012

**1.3.3      Debarment Certification**

Genentech, 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 for the investigation of product vismodegib in connection with this New Drug Application at Genentech, Inc.

Signed by:



Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs

09/08/2011

Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203388 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: ERIVEDGE Established/Proper Name: vismodegib Dosage Form: capsule		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Mona Patel		Division: Division of Oncology Products 2
<p><b>NDA Application Type:</b> <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p><b>Efficacy Supplement:</b> <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><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> 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><b><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></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>		
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>March 8, 2012</u></li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• <input checked="" type="checkbox"/> None</li> </ul>		
<ul style="list-style-type: none"> <li>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?            Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</li> </ul>		<input type="checkbox"/> Received

<sup>1</sup> 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 <sup>2</sup>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority          Chemical classification (new NDAs only): Type 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input 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>           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 checked="" type="checkbox"/> REMS not required         </p> <p>Comments: Genentech proposed a REMS in the 9/8/11 original application, but after review DOP2 determined a REMS was not required for this drug product.</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 checked="" type="checkbox"/> Other ASCO Burst

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. 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"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>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></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>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></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	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"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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></li> </ul>	<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 <sup>3</sup>	1.30.12
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval 1.30.2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	1/27/12 GNE Proposed Final Draft Labeling
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	9/8/2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<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"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	1/27/2012 GNE Final Draft Label
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	9/8/2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	12/22/2011 final draft labeling
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i></li> </ul> </li> </ul>	11/28/11 Acceptability Letter 11/28/11 DMEPA Review
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM PLR Format Labeling Review w/secondary concurrence 11/15/11 <input checked="" type="checkbox"/> DMEPA 12/6/11 <input checked="" type="checkbox"/> DRISK (Patient Labeling) 12/20/11 <input checked="" type="checkbox"/> DDMAC (OPDP)1/12/12, 12/23/11, 12/19/11,12/7/11 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MHT: Primary Review w/secondary and tertiary review 1/9/12
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	Filing Review/Memo of Filing Meeting w/secondary concurrence 11/4/11  <input checked="" type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>11.16.2011</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)</li> </ul>	<p>FDA Prop. Change to USPI &amp; MG 1/27/12  Telecon 1.26.12  FDA Prop. Changes to USPI and MG 1/24/12  FDA Advice 1/19/12  FDA Advice 1/13/12  FDA Advice 1/13/12  FDA Advice 1/12/12  FDA Pro. Changes to USPI 1/11/12  Telecon 1/11/12  FDA Request 1/11/12  FDA Changes to MG 1/9/12  FDA Req for Info 1/6/12  FDA Advice 1/3/12  FDA Req for Info 12/30/11  CMC AI LTR 12/19/11  FDA Request for Info 12/16/11  FDA Pro. Changes to USPI 12/14/11  Telecon (Risk Mgmt Strategy) 12/13/11  FDA Request for Info 12/9/11  FDA Advice 12/9/11  FDA Req. for Info 11/30/11  74 Day Ltr 11/17/2011  Clin.Pharm Request 11/16/11  CMC AI LTR 11/16/11  60 Day Letter 11/4/11  Clin.Pharm Request 11/1/2011  Pharmacometric Req. 10/25/11  Telecon Summary 10/20/11  FDA Request for Info 10/19/11  CMC Request 10/11/11  Clin.Pharm Request 10/11/11  DRISK/MHT Request 10/7/11  CP,NC &amp;Micro Request 10/5/11  Telecon (DSI) 9/28/2011  Clinical Request 9/27/11  Clin.Pharm Request 9/26/11  ACK LTR 9/22/11  AOP Advice 9/21/11</p>
<ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>	<p>Labeling Meeting 1/18/12  Labeling Meeting 1/11/12  Wrap Up Meeting 1/5/12  Labeling Meeting 1/5/12</p>

	<p>Team Meeting 12/12/11 Labeling Meeting 12/12/11 Labeling Meeting 12-9-11 Team Meeting 12/5/11 Labeling Meeting 12-2-11 Team Meeting 12-1-11 Labeling Meeting 11-30-11 Labeling Meeting 11-29-11 Team Meeting 11-29-11 Mid-Cycle Meeting 11/21/11 Team Meeting 11/18/11 Team Meeting 11/14/11 Team Meeting 11/4/11 Priority Review Memo 11/3/11 Team Meeting 10/26/11 Team Meeting 10/24/11 Team Meeting 10/12/11 Second Planning Meeting 9/27/2011 Planning Meeting 9/20/2011</p>
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 12.9.2011
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 5/11/11 5/10/11 CMC
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	7/9/10 Toxicology/Pharmacology (mtg cancelled, respo sent 7/6/10) 4/29/09 CMC (min. issued 9/28/09) 4/28/08 EOP1 (min issued 7/6/08)
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/30/12
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/24/12
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/13/12
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 7
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	Primary Review w/ secondary concurrence 1/13/12

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

	Filing Review w/secondary concurrence 9/30/11
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (indicate date for each review)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>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 (indicate date of review/memo)</li> </ul>	located on page 24 of primary review 1/13/12
<ul style="list-style-type: none"> <li>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (indicate date(s) of submission(s))</li> <li>REMS Memo(s) and letter(s) (indicate date(s))</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</li> </ul> </li> </ul>	GNE Proposed REMS 9/8/11  <input type="checkbox"/> None Primary Review w/secondary concurrence 1/13/12
<ul style="list-style-type: none"> <li>DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)</li> </ul>	<input type="checkbox"/> None requested 1/27/12 VAI 1/20/12 VAI 12/12/11 w/secondary & tertiary concurrence
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> <li>Clinical Microbiology Team Leader Review(s) (indicate date for each review)</li> </ul>	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>Statistical Division Director Review(s) (indicate date for each review)</li> </ul>	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None Primary Review w/secondary and tertiary review 1/6/12 Filing Review w/secondary concurrence 10/4/11
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>Clinical Pharmacology Division Director Review(s) (indicate date for each review)</li> </ul>	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None Addendum to Primary Review 1/12/12 Primary Review w/secondary concurrence 1/6/12 QT-IRT Review 11/30/11 Filing Review w/secondary concurrence 10/5/2011
<ul style="list-style-type: none"> <li>DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)</li> </ul>	<input checked="" type="checkbox"/> None

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Tertiary Review 1/13/12 Secondary Review 1/13/12
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Addendum to Primary Review w/secondary concurrence 1/24/12 Primary Review w/secondary concurrence 1/13/12 Filing Review w/secondary concurrence 10/4/2011
❖ 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
<b>Product Quality</b> <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 1/23/12
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/30/12
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Primary Review (DS) w/secondary concurrence 1/20/12 Primary Review (DP) w/secondary concurrence 1/20/12 Filing Review (ONDQA Biopharm) w/secondary concurrence 10/19/11 Filing Review (Product) w/secondary concurrence 10/7/11
❖ Microbiology Reviews <input checked="" 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 (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed 12.21.2011 w/secondary concurrence Filing Review w/secondary concurrence 9/30/2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 1/18/12 Statistical
❖ 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> )	9/28/11
<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) (date completed must be within <b>2 years</b> of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites <sup>6</sup> )	Date completed: 1/24/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>6</sup> 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.

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

MONA G PATEL  
01/31/2012



NDA 203388

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Genentech  
Attention: Mary Sliwkowski  
1 DNA Way MS#241B  
South San Francisco, CA 94080-4990

Dear Mary Sliwkowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Erivedge (Vismodegib), capsules, 150 mg.

We will be performing methods validation studies on Erivedge (Vismodegib), capsules, 150 mg, as described in NDA 203388.

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

**Methods, current version**

(b) (4) Identity, assay, and degradation products of Vismodegib drug product by HPLC [Vismodegib, capsules, 150 mg, Genentech, Inc.]”.

**Samples and Reference Standards**

60 capsules Vismodegib 150 mg  
200 mg Vismodegib Reference Standard

(b) (4)

(b) (4)

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

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: Michael L. Trehy  
1114 Market Street, Room 1005A  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
Chemist  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHAEL L TREHY  
01/27/2012

**From:** Patel, Mona  
**Sent:** Friday, January 27, 2012 4:34 PM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Proposed Final Draft Labeling ERIVEDGE (vismodegib) NDA 203388

**Attachments:** FDA Proposed Change Vismodegib 1.27.12 (Proposed Draft Final Labeling (USPI & MG).doc)

Sarah,

We accepted your January 26, 2012 response to the US package insert and made one edit to the Medication Guide.

Attached is FDA proposed Final Draft Labeling. If you accept our change, please submit formally today as an amendment to NDA 203388 identifying in the header of your cover letter, FINAL DRAFT LABELING.

Please ack receipt.

Mona



FDA Proposed  
Change Vismodegib..

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

☎ 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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MONA G PATEL  
01/27/2012



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

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Telecon Minutes

**Meeting Date:** January 26, 2012

**From:** Mona Patel, Pharm.D., DOP2/OHOP/OND/CDER/FDA

**Subject:** Telecon w/ Genentech to discuss January 26, 2012 submission containing a response to FDA proposed changes dated January 24, 2012 on the USPI and Medication Guide

**Product:**

vismodegib (NDA 20338); Indication: for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

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FDA Attendees:

Mona Patel, Pharm.D., Regulatory Health Project Manager, OHOP/DOP2  
Patricia Keegan, M.D., Director, OHOP/DOP2  
Jeff Summers, M.D., Deputy Director of Safety, OHOP/DOP2  
Michael Axelson, M.D., Clinical Reviewer, OHOP/DOP2  
Melissa Tassinari, Ph.D., Acting Team Leader, PMHS-MHT  
Sharon Mills, BSN, RN, CCRP., Senior Patient Labeling Reviewer, DMPP/OMPI  
Karen Munoz, **BSN, RN., Consumer Reviewer, OPDP/DDTCP**

Genentech Attendees:

Jennifer Low, M.D., Ph.D. Group Medical Director, Global Development Team Leader, Product Development Oncology  
Sarah Wayson, Ph.D. Regulatory Scientist, Product Development Regulatory  
Wen Liu, Ph.D. Vismodegib Global Regulatory Lead, Product Development Regulatory  
Israel Gutierrez, M.D. Senior Global Safety Science Lead  
Howard Mackey, Ph.D. Senior Statistical Scientist, Product Development  
Josina Reddy, M.D., Ph.D. Senior Medical Director, Product Development Oncology  
Nathan Winslow, Associate Director, Product Development Regulatory

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**Purpose:** FDA requested this teleconference with Genentech to discuss January 26, 2012 submission containing a response to FDA proposed changes dated January 24, 2012 on the USPI and Medication Guide

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**Discussion:** FDA initiated the discussion by informing Genentech that the intent of the telecon was to reach agreement on outstanding issues with USPI and MG.

*Section 1 Indications And Usage*

In the rationale document which was included in the January 26, 2012 submission, Genentech proposed 3 options for FDA to consider for the wording of the indication statement. FDA chose option 3 which reads, ERIVEDGE capsule is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. Genentech acknowledged.

*Section 8.6 Females of Reproductive Potential and Males*

In the FDA proposed change dated 1.24.12, FDA deleted (b) (4) In the January 26, 2012 submission, Genentech's response to FDA's proposed change was (b) (4)

(b) (4) Genentech further responded that in clinical trials, 3 out of 10 women of childbearing potential developed amenorrhea while receiving Erivedge, and this adverse event may obscure an unrecognized pregnancy. Genentech cited the labels for other teratogens, including thalidomide, lenalidomide, bexarotene, and ambrisentan (b) (4)

(b) (4) Genentech agreed to remove language (b) (4)

*Section 14 Clinical Studies*

In the FDA proposed change dated 1.24.12, FDA informed Genentech that the definition of complete response (CR) was not properly defined as in Appendix C of the application. In the January 26, 2012 submission, Genentech provided a rationale on the proposed

definition of CR in the revised labeling, based on the non-standard but protocol-specified definition of a CR. At the end of the discussion, FDA agreed with Genentech's justification and agreed to include the complete response definition in the USPI. FDA requested Genentech include a footnote to table 2 of the USPI defining CR as this definition is non-standard. Genentech agreed to do so. FDA also sought agreement from Genentech that for promotional purposes, the table would not be extracted without the footnote. Genentech agreed.

#### Medication Guide

Genentech agreed to update the Medication Guide per the agreements reached on the USPI.

Discussion occurred for language under header "What is Erivedge?"

FDA and Genentech discussed modification of this section for consistency with the USPI. The proposed language under this section was to read, *ERIVEDGE is a prescription medicine used to treat adults with a type of skin cancer, called basal cell carcinoma, that has spread to other parts of the body or that has [REDACTED] (b) (4) [REDACTED] come back after surgery or your healthcare provider has decides it cannot be treated with surgery or radiation.*

*It is not known if ERIVEDGE is safe and effective in children.*

Discussion also occurred for Genentech's response to list [REDACTED] (b) (4) as a separate statement under the header "What are the possible side effects of ERIVEDGE?." FDA did not agree with Genentech's proposal as the number of events were small and insufficient data were obtained in the trial to characterize and confirm such risks. Genentech agreed to delete.

Genentech stated they would send revised labeling to FDA for review by 5pm EST. Before call concluded, Genentech asked for an update on the proposed action date. FDA stated their intent to take action soon.

Call concluded.

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/s/  
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MONA G PATEL  
01/30/2012

**From:** Patel, Mona  
**Sent:** Tuesday, January 24, 2012 5:11 PM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Proposed Changes to USPI & MG: NDA 203388 ERIVEDGE (vismodegib)

**Attachments:** FDA Proposed Changes Vismodegib Medication Guide 1 24 12.doc; FDA Proposed Changes Vismodegib USPI 1-24-12.doc

Sarah,

I have attached FDA proposed changes to the USPI and MG for ERIVEDGE (vismodegib) under NDA 203388. Please provide us a response by 5:15pm EST, Wednesday, January 25, 2012.

Please acknowledge receipt.

Mona



FDA Proposed  
Changes Vismodegi.



FDA Proposed  
Changes Vismodegi..

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

☎ 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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MONA G PATEL  
01/24/2012

**From:** Patel, Mona  
**Sent:** Thursday, January 19, 2012 11:56 AM  
**To:** 'Sarah Wayson'  
**Subject:** RE: vismodegib NDA203388: GNE response to FDA-proposed changes to USPI  
Sarah,

We cannot commit to action on a certain date. It is possible that action could occur prior to the PDUFA date, including prior to 2/3/12. Regarding labeling, any printing of labeling prior to FDA action on the application is at your risk. We cannot commit to a date at which it is "less risky" for you to print.

Mona

---

**From:** Sarah Wayson [mailto:wayson.sarah@gene.com]  
**Sent:** Friday, January 13, 2012 4:54 PM  
**To:** Patel, Mona  
**Subject:** Re: vismodegib NDA203388: GNE response to FDA-proposed changes to USPI

It's an interesting story... yes, let's discuss Tuesday. I had to get IT support to help figure it out :-)

It would be great if we could touch base briefly Tuesday to discuss timeline for remaining activities. I continue to get two questions, nearly hourly now, from my team:

- 1) Is there any chance that FDA would take action prior to Feb 3? (I know you previously told me no.)
- 2) Is there any chance we could have the USPI essentially finalized and be able to print at risk in advance of the action date. This stems from the fact that we have about a 10-14 day timeline for printing and packaging, so the team is concerned with having product available in the event of an approval. We understand that any printing in advance is at our own risk, but would like to understand if there might be a point at which it will be "less risky." I would appreciate being able to discuss with you by phone.

Thanks so much and have a good weekend.  
Sarah

Sarah Wayson, PhD | Scientist, Product Development Regulatory - Program Management | Genentech, Inc., A Member of the Roche Group | desk: 650-225-7928 | mobile: 650-238-8736

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MONA G PATEL  
01/31/2012



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

Memorandum

**Date:** January 13, 2012

**From:** Mona Patel, Pharm.D., DOP2/OHOP/OND/CDER/FDA

**Subject:** FDA Comments from OPDP on draft (b)(4) submitted on 1.5.2012

**Product:** NDA 203388: ERIVEDGE (vismodegib)

FDA has completed its review of the draft (b)(4) included in your January 5, 2012 submission. We have the following suggested edits that you are at liberty of accepting or declining.

(b)(4)

**Mailing of Important Information about Drugs**

2. Refer to 21 CFR § 200.5 (Mailing of important information about drugs) regarding the format for recommended mailing of important information regarding drug warnings. We recommend that the distinctive box described in 21 CFR § 200.5 appear in the letter as well as on the envelope.

**Prescribing Information (PI)**

3. Please ensure that all information in this proposed (b)(4) is revised to be consistent with the PI once an approved version is available.

**SPECIFIC COMMENTS**

4. We recommend that the proposed (b)(4) be updated in accordance with the draft guidance (b)(4) dated November 2010.

The proposed (b) (4) for ERIVEDGE is intended (b) (4) (b) (4)

5. We recommend the following (b) (4) to improve communication (b) (4), consistent with the guidance (please note that this list is not all inclusive):

(b) (4)



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MONA G PATEL  
01/13/2012



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

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Memorandum

**Date:** January 13, 2012

**From:** Mona Patel, Pharm.D., DOP2/OHOP/OND/CDER/FDA

**Subject:** Clinical Pharmacology Comments on exploratory analysis submitted on 1.10.2012

**Product:** NDA 203388: ERIVEDGE (vismodegib)

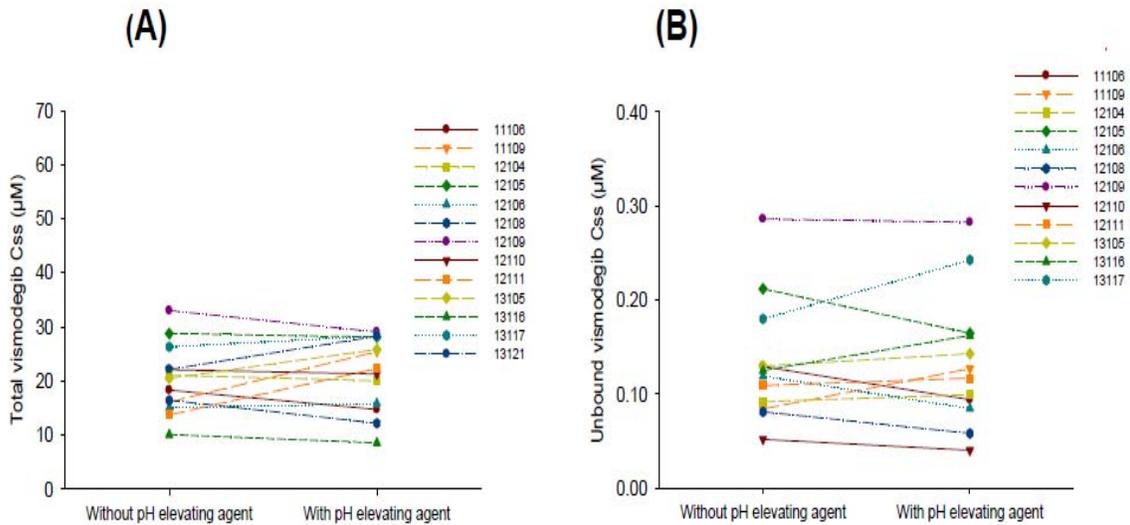
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FDA has completed its review of your January 10, 2012 submission containing your exploratory analysis of the impact of pH altering drugs on systemic exposure of vismodegib. We have the following clinical pharmacology comments which were previously conveyed to you at the 1.11.12 telecon.

1. The plots for each patient who took a pH elevating agent and had relevant PK data for a visual comparison of pre- and post-administration of a pH elevating agent are not provided. Using the average PK data for the comparison between patients with and without pH altering agents may mask an effect of such agents on vismodegib exposure.
2. The retrospective and exploratory PK analysis on limited number of patients could not rule out the possible effects of pH elevating agents on vismodegib exposure. For example, there are large variations of the dose intervals between pH elevating agents and vismodegib. There is also considerable variability for the PK sampling time.
3. The analysis should separate the three classes of agents as PPI, H<sub>2</sub> blockers and antacids because PPI/H<sub>2</sub> blockers have prolonged effect and high potency regarding the pH elevation relative to antacids.
4. We have identified some inconsistencies between the Figure 2 and Table 2 in your document submitted on 01/10/2011. For example, Table 2 (below) shows that Patient 13116 had the largest increase in concentration when vismodegib was administered with a pH-elevating agent, but Figure 2 (below) shows that this

patient had a decrease in vismodegib concentration when vismodegib was administered with a pH-elevating agent.

**Figure 2: Intra-Patient Steady-State Concentrations of Total (A) and Unbound (B) Vismodegib for Patients Taking a pH Elevating Agent Concomitantly with Vismodegib**



**Table 2: Intra-Patient Fold Change in Vismodegib Total  $C_{ss}$  and AAG Post- and Pre-administration of a pH Elevating Agent**

Subject ID	Fold Change in Vismodegib Mean $C_{ss}$	Fold Change in Mean AAG
13116	1.62	1.57
12104	1.58	1.15
14121	1.28	NA
13117	1.26	1.13
14112	1.08	1.01
12108	1.06	1.14
12106	0.98	1.11
13105	0.96	NA
12105	0.95	1.04
12111	0.88	0.90
13121	0.85	0.96
11106	0.80	1.04
12109	0.74	0.90

NA: AAG concentration not measured in this patient at the relevant timepoint.

Note: Values >1.0 indicate an increase in concentration when vismodegib was administered with a pH-elevating agent, relative to when vismodegib was given alone in the same patient. Similarly, values <1.0 indicate a decrease in concentration.

5. The high protein binding to both human serum albumin and alpha-1 acid glycoprotein (AAG) does not rule out the possible effects of pH on vismodegib solubility and bioavailability. For example, binding of dasatinib to human plasma protein was 96%. Erlotinib is approximately 93% protein bound to plasma albumin and AAG. The bioavailability of both drugs is affected by pH elevating agents. In addition, the mechanism for the observed correlation between AAG levels and total vismodegib concentrations but not the unbound concentrations is not clear.
6. The co-medication listing in the Appendices received January 10, 2012 is not consistent with the co-medication listing provided in the NDA submission.

*Other considerations:*

7. The solubility of vismodegib is pH dependent and the difference is 10000-fold between pH 7 (0.1µg/mL) and pH 1 (990 µg/mL).
8. pH dependent solubility has been seen in several other drugs such as dasatinib, erlotinib and nilotinib. For dasatinib and erlotinib, *in vivo* studies have been conducted and the results led to the labeling recommendations on how to dose those agents. For nilotinib, a PMR has been issued.
9. The potential effect of pH elevating agents on vismodegib absorption is suggested by a PopPK analysis. The  $k_a$  is 9.025 and 17.65 day<sup>-1</sup> in cancer patients and healthy subjects, respectively. As you stated in the original NDA submission, the slower absorption in patients may be due to multiple factors such as slower gastrointestinal (GI) transit, higher GI pH, and co-medications affecting GI conditions, which in turn may affect vismodegib solubility and absorption *in vivo*.
10. FDA exploratory analysis:

Table 1 contains the FDA exploratory analysis of the primary efficacy endpoint from the registration trial SHH4476g. A trend towards lower objective response is observed among patients with locally advanced disease BCC who have been systemically exposed to a pH elevating agent while on vismodegib treatment, and a similar trend is observed for patients with metastatic BCC.

It is noted that this analysis is exploratory and could not exclude the confounding factors because of the nature of a single-arm trial. Nevertheless, this exploratory analysis provides supportive evidence for the necessity of a dedicated study on pH elevating agents.

**Table 1: Objective Response by Exposure to pH Elevating Agents: Efficacy  
Evaluable patients in SHH4476g**

Systemic Exposure to pH elevating agents	Metastatic BCC		Locally Advanced BCC		All Patients	
	n	Responders (%)	n	Responders (%)	n	Responders (%)
Yes	11	3 (27.2%)	16	4 (25.0%)	27	7 (25.9%)
No	22	7 (31.8%)	47	23 (48.9%)	69	30 (43.5%)
All Patients	33	10 (30.3%)	63	27 (42.9%)	96	37 (38.5%)

Taken together, FDA continues to request for a dedicated clinical trial as a PMR to evaluate if pH altering agents change the bioavailability of vismodegib. You may study the worst case scenario first in healthy volunteers, and then determine if further studies on other classes of gastric pH elevating agents are necessary. The study results should allow for a determination on how to dose vismodegib with regard to these gastric pH elevating agents.

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MONA G PATEL  
01/13/2012

**From:** Patel, Mona  
**Sent:** Thursday, January 12, 2012 10:29 AM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Comments from Maternal Health Team: NDA 203388

1. Regarding question 2 of the patient guided questionnaire, consider using the term "vasectomy (male patients)" (b) (4)  
[Redacted]
2. Consider combining questions 2 and 3 of the patient guided questionnaire, (b) (4)  
[Redacted]
3. Consider modification of question 8 of the patient guided questionnaire. (b) (4)  
[Redacted]  
Consider rephrasing the question to ask "Who advise you of the risk before taking vismodegib?"

4. A note to the sponsor:

We have reviewed the rationale for the anticipated number of possible pregnancies per year and note that this calculation is a best case scenario. The sponsor assumes that 1.5% of the approximately 680 females of reproductive potential (about 10 each year) may become pregnant and that their plan for active pregnancy prevention education will lead to a 10% reduction in the number of unintended pregnancies (1 per year). That estimate was increased to 2 per year to account for possible pregnancies in female partners of men treated with vismodegib. Using the sponsor's rationale, if the plan for active pregnancy prevention education does not work as anticipated, one might assume that there would be up to 10 pregnancies per year, with a range of 2-10 per year and up to 100 pregnancies over a ten year period.

Please provide a response via email followed by formal when you have addressed all issues surrounding the program.

Please email me your response by COB Tuesday, January 17, 2012

**Please ack receipt.**

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993  
☎ 301.796.4236 (phone) • 301.796.9849 (fax) | mona.patel@fda.hhs.gov (email)



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MONA G PATEL  
01/12/2012



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Center for Drug Evaluation and Research

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Telecon Minutes

**Meeting Date:** January 11, 2012

**From:** Mona Patel, Pharm.D., DOP2/OHOP/OND/CDER/FDA

**Subject:** Telecon w/ Genentech to discuss January 5, 2012 submission on pregnancy pharmacovigilance program and January 10, 2012 submission regarding organ dysfunction study as PMR

**Product:**

vismodegib (NDA 20338); proposed indication “for the treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and (b) (4) who are not candidates for radiation.

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FDA Attendees:

Mona Patel, Pharm.D., Regulatory Health Project Manager, OHOP/DOP2  
Karen Jones, M.S., Chief, Project Management Staff, OHOP/DOP2  
Jeff Summers, M.D., Deputy Director of Safety, OHOP/DOP2  
Michael Axelson, M.D., Clinical Reviewer, OHOP/DOP2  
Hong Zhao, Ph.D., Supervisory Clinical Pharmacologist, OTS/OCP/DCPV  
Jian Wang, Ph.D., Clinical Pharmacologist, OTS/OCP/DCPV  
Amarilys Vega, M.D., M.P.H, Reviewer, OSE/DRISK  
Melissa Tassinari, Ph.D., Acting Team Leader, PMHS-MHT  
Robert Pratt, Pharm.D. Team Leader Safety Evaluator, OSE/DPV2

Genentech Attendees:

Sarah Wayson, Ph.D., Regulatory US Partner for vismodegib, Product Development Regulatory  
Jennifer Low, M.D., Ph.D., Global Development Team Lead for vismodegib & Group Medical Director, Product Development Oncology  
Wen Liu, Ph.D., Global Regulatory Lead for vismodegib, Product Development Regulatory  
Michelle Rohrer, Ph.D. Vice President, US Product Development Regulatory  
Josina Reddy, M.D., Ph.D., Senior Medical Director, Product Development Oncology  
Israel Gutierrez, M.D. Senior Global Safety Science Lead, Oncology, Global Risk

## Management

Ron Magana, Manager, U.S. Pharmacovigilance

Howard Mackey, Ph.D. Senior Statistical Scientist, Product Development

Lisa Wang, ScD, MPH, Senior Epidemiologist, Epidemiology, Patient Reported Outcomes & Healthcare Data Strategy

Richard Graham, Ph.D., Clinical Pharmacology and Nonclinical Team Lead

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**Purpose:** FDA requested this teleconference with Genentech to discuss Genentech's response submitted on January 5, 2012 on the revised risk management strategy requested during the December 13, 2011 teleconference and the January 10, 2012 submission containing Genentech's response on FDA's request to conduct a clinical trial on organ dysfunction.

**Background:** On September 8, 2011, Genentech submitted NDA 203388 for vismodegib (b) (4)

On October 20, 2011, FDA held a telecon with Genentech to discuss Genentech's proposed (b) (4) submitted with the September 8, 2011 initial NDA. At the conclusion of the October 20, 2011 telecon, it was agreed that Genentech would submit a revised risk management strategy in communicating the potential risks of embryo-fetal toxicities associated with vismodegib and would describe in detail the specific objectives or goals. Genentech submitted their revised risk management proposal on November 4, 2011 with accompanying draft supporting materials submitted on November 18, 2011. FDA requested a teleconference with Genentech for December 13, 2011 to discuss Genentech's November 4, 2011 submission on the revised risk management proposal. During the teleconference, FDA informed Genentech that a postmarketing requirement (PMR) on the enhanced pregnancy surveillance and reporting would be necessary to support approval of vismodegib and asked Genentech to submit PMR language along with milestones for FDA to review. Genentech responded to FDA's request on January 5, 2012. FDA requested a teleconference with Genentech for January 11, 2012 to discuss Genentech's response. Prior to the teleconference, FDA conveyed to Genentech for consideration, proposed changes to the draft PMR language submitted in the January 5, 2012 submission (copied below). FDA also had comments to share on Genentech's response to FDA's request to conduct a clinical trial as a PMR to evaluate if pH elevating agents (e.g. H2 antagonists, proton pump inhibitors and antacids) alter the bioavailability of vismodegib. Genentech's January 10, 2012 response included an exploratory analysis on the effects of pH elevating agents on vismodegib pharmacokinetics with the data retrospectively collected from clinical trials.

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**From:** Patel, Mona  
**Sent:** Wednesday, January 11, 2012 10:26 AM  
**To:** 'Sarah Wayson'  
**Subject:** Draft PMR Language: NDA 203388 (vismodegib) (Pregnancy)

Sarah,

Please share with your team prior to our telecon.

Mona

Conduct a Pregnancy Pharmacovigilance Program to evaluate pregnancy outcomes and infant outcomes following exposure to vismodegib. This program will include a mechanism to collect, classify and analyze data on direct exposures (women exposed to vismodegib as treatment) and indirect exposures, (women exposed to vismodegib through the seminal fluid of a male partner. The Pregnancy Pharmacovigilance program will, at a minimum, include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Specific program objectives
- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively
- Description of patient contact and follow up efforts
- Description of plan to communicate program existence (Patient and HCPs) and description of plan to evaluate the effectiveness of the program
- Description of plan for discontinuation of the program
- Submission of a stand-alone report of cumulative program outcomes data to the Agency

The timetable you submitted on **DATE**, states you will conduct this PMR according to the following schedule:

Initiation of Program: launch.	At the time of product launch.
Final Protocol and analysis plan submission:	March 2012
Annual Interim Report Submission for ten years:	<b>Applicant to Provide Date</b>
Final Report Submission:	<b>Applicant to Provide Date</b>

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## Discussion:

FDA initiated the discussion asking Genentech if they had any questions on the FDA proposed changes to the draft PMR language (attached above) for the pharmacovigilance program. Genentech sought clarification on the expectations of the PMR and specifically asked for clarification of definitions of the terms “prospectively” and “retrospectively”. FDA referred Genentech to the Guidance for Industry – Establishing Pregnancy Exposure Registries (2002). Genentech requested to replace the word **(b) (4)** with ‘plan’ in the draft PMR language to which FDA agreed to. Genentech asked if the January 5, 2012 submission containing a revised risk management proposal

encompassing a draft HCP letter, draft physician brochure, and draft PMR language for a pregnancy pharmacovigilance plan had any major gaps for Genentech to consider revising. FDA responded that overall the approach Genentech was taking seemed appropriate. FDA informed Genentech that comments from the maternal health team would be forthcoming.

FDA suggested Genentech re-consider extending the time for the final plan submission to ensure by the submit date that the plan was complete; however, the program is expected to be operational at the time of product launch. Genentech suggested May 2012 as a more appropriate date

*Regarding January 10, 2012 Submission:*

After review of Genentech's January 10, 2012 submission as outlined above, FDA informed Genentech that FDA will still continue to request for a dedicated clinical trial as a PMR to evaluate if pH altering agents change the bioavailability of vismodegib. FDA further informed Genentech that Genentech may study the worst case scenario first in healthy volunteers, and then determine if further studies on other GI pH elevating drugs are necessary. The study results should allow for a determination on how to dose vismodegib with regard to these gastric pH elevating agents. FDA suggested that for example, separating the doses between those drugs and EVRIEDGE by several hours may be an option of practical solutions. Genentech agreed to propose milestone timelines for the PMR to study the effect of gastric pH elevating agents on vismodegib bioavailability. FDA suggested that the sponsor could study the worst case scenario first and the results will determine whether additional studies are required. Genentech agreed to submit the draft protocol for FDA review and comment.

With regard to the proposed organ dysfunction PMR studies, FDA agreed with Genentech's proposal to remove [REDACTED] (b) (4) [REDACTED] from the PMR language. However, FDA reminded the sponsor to follow the pertinent FDA guidance and make efforts to balance age, gender and body weight among study arms to reduce inter-subject variability. FDA informed Genentech that detailed comments regarding the January 10, 2012 submission would be forthcoming. FDA requested that Genentech submit a proposal for milestones for the organ dysfunction study and an updated proposal on milestones for the pregnancy pharmacovigilance program. Genentech agreed to do so.

Call concluded.

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/s/  
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MONA G PATEL  
01/23/2012

**From:** Patel, Mona  
**Sent:** Wednesday, January 11, 2012 4:58 PM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Proposed Changes to ERIVEDGE (vismodegib) labeling NDA 203388

Sarah,

Attached are FDA's proposed changes to the USPI made in response to your 12.21.2011 response. Please ack receipt.

FYI: Please check spacing and formatting  
Highlights will be revised once we have reached final agreement on FPI

Please provide us your response to USPI and MG by 11am EST, Tuesday January 17, 2012.

Mona



FDA Proposed  
Changes Vismodegi..

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/s/  
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MONA G PATEL  
01/12/2012

**From:** Patel, Mona  
**Sent:** Wednesday, January 11, 2012 10:26 AM  
**To:** 'Sarah Wayson'  
**Subject:** Draft PMR Language: NDA 203388 (vismodegib) (Pregnancy)  
Sarah,

Please share with your team prior to our telecon.

Mona

Conduct a Pregnancy Pharmacovigilance Program to evaluate pregnancy outcomes and infant outcomes following exposure to vismodegib. This program will include a mechanism to collect, classify and analyze data on direct exposures (women exposed to vismodegib as treatment) and indirect exposures, (women exposed to vismodegib through the seminal fluid of a male partner. The Pregnancy Pharmacovigilance program will, at a minimum, include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Specific program objectives
- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively
- Description of patient contact and follow up efforts
- Description of plan to communicate program existence (Patient and HCPs) and description of plan to evaluate the effectiveness of the program
- Description of plan for discontinuation of the program
- Submission of a stand-alone report of cumulative program outcomes data to the Agency

The timetable you submitted on **DATE**, states you will conduct this PMR according to the following schedule:

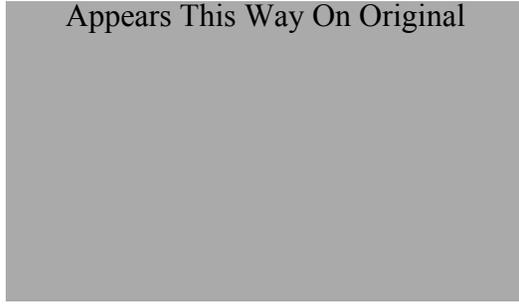
Initiation of Program: launch.	At the time of product
Final Protocol and analysis plan submission:	March 2012
Annual Interim Report Submission for ten years:	<b>Applicant to Provide Date</b>
Final Report Submission:	<b>Applicant to Provide Date</b>

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

☎ 301.796.4236 (phone) • 301.796.9849 (fax) | mona.patel@fda.hhs.gov (email)

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/s/  
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MONA G PATEL  
01/11/2012

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From: Patel, Mona  
Sent: Monday, January 09, 2012 2:18 PM  
To: 'Sarah Wayson'  
Subject: FDA Proposed Changes to Medication Guide (NDA 203388 vismodegib (ERIVEDGE))

Sarah,

I have attached FDA proposed changes to the Medication Guide for vismodegib under NDA 203388. Please email us your response (clean and redlined) along with your formal submission by 8am EST Tuesday, 1.17.12.

FYI: Our office is closed Monday, 1.16.2012 for MLK Day.

Please confirm receipt.

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

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/s/  
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MONA G PATEL  
01/09/2012

**From:** Patel, Mona  
**Sent:** Friday, January 06, 2012 1:43 PM  
**To:** 'Sarah Wayson'  
**Cc:** Mesmer, Deborah  
**Subject:** FDA IR (CMC): NDA 203388  
Sarah,

On behalf of CMC team, I am forwarding to you 3 requests. Please provide a response via email (followed by formal submission) by 2pm EST Tuesday, January 10, 2012.

Please ack receipt.

Mona

**Drug Substance Specifications:**

1. The proposed acceptance criteria for total impurities in the drug substance (b)(4) is not supported by clinical lot history (b)(4) (b)(4) this acceptance criteria.
2. The proposed acceptance criteria for individual unspecified impurities (b)(4) (b)(4) the identification limit of 0.10% for a 150mg daily dose, per ICH Q3A. Revise this acceptance criteria to conform to ICH Q3A .

**Drug Substance Manufacturing Process:**

3. The proposed approach to control the drug substance manufacturing process within Proven Acceptable Range (PAR) values is not adequately supported by the data provided in your submission. However, Normal Operating Ranges (NOR) appear to be reasonable and may be included in the process description. Revise the drug substance manufacturing process description to reflect the above changes.

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

☎ 301.796.4236 (phone) • 301.796.9849 (fax) | mona.patel@fda.hhs.gov (email)



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MONA G PATEL  
01/06/2012

**eCTD NDA 203388/0**  
**vismodegib (Erivedge)**  
**Wrap Up Meeting Summary**  
**1-5-12**

Memorandum

**Date:** January 5, 2012

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Wrap Up Meeting Agenda: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]

**Submission Date:** September 8, 2011

**Received Date:** September 8, 2011

**Sponsor:** Genentech, Incorporated

**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

**Current Review Team for NDA 203388:**

*Director:*

Patricia Keegan

*Regulatory:*

Mona Patel, Regulatory Project Manager

Karen Jones (CPMS)

*Clinical:*

Michael Axelson

Jeff Summers (CDTL)

*Statistical:*

Janet Xiaoping Jiang

Kun He (TL)

*Clinical Pharmacology:*

Jian Wang

Hong Zhao (TL)

Christian Grimstein (Pharmacogenomics)

Bahru Habtemariam (Pharmacometrics)

*Toxicology:*

Dubravaka Kufrin

Todd Palmby (TL)

*Product:*

Anne Marie Russell  
Zedong Dong  
Liang Zhou (TL)  
Youngsook Jean (Biometrics)

**Consults:**

- |    |                             |   |
|----|-----------------------------|---|
| a. | OPDP Reviewers              | Carole Broadnax - professional reviewer,<br>Karen Munoz - consumer reviewer |
| b. | DSI Clinical Reviewer       | Lauren Iacono-Connor  |
| c. | OSE (DRISK) Reviewer (REMS) | Amarilys Vega   |
| d. | DMEPA                       | Rick Abate- Safety Evaluator  |
| e. | Maternal Health:            | Tammie B. Howard  |
| f. | Facility Reviewers:         | Mahesh Ramanadham   |
| g. | Microbiology Consult:       | John Metcalfe   |
| h. | BioPharma Consult:          | Zedong Dong   |
| i. | QT-IRT Consult              | Devi Kozeli   |

**Agenda Items:**

1. **Milestones/Updates:**  
Planning Meetings Held: September 20 & 27, 2011  
Filing Meeting Held: October 4, 2011  
Mid-Cycle Meeting: November 18, 2011  
Labeling Meetings Held: November 29, November 30, December 2, December 9,  
December 12  
Action Letter: Will circulate by January 5, 2012 and send to Jeff by January 13,  
2012  
Action Package: Will circulate by January 6, 2012
2. **Review Timeline:**  
Primary Reviews Due (in darrrts): January 6, 2012;  
Secondary Reviews Due (in darrrts): January 10, 2012; January 20, 2012 (CMC)  
CDTL Reviews Due (in darrrts): January 13, 2012  
DD Review Due (in darrrts): January 24, 2012  
OD Review Due (in darrrts): February 3, 2012  
Final Action Due: March 8, 2012 (targeting February 3, 2012)
3. Review Status/Issues:

- a. Clinical: *No outstanding issues*
  - b. Nonclinical: *Tertiary signature needed. Review should have final signatures by January 10, 2012*
  - c. CMC/Biometrics: *Review will be uploaded by the morning of January 20, 2012*
  - d. Clinical Pharmacology/ Pharmacometrics/ Pharmacogenomics: *Awaiting results of GNE's evaluation of clinical PK data to evaluate impact on pH altering drugs on steady-state concentrations of vismodegib.*
  - e. Maternal Health: *Deemed GNE's 1.5.2012 response to 12.13.11 telecon requesting revised risk management proposal acceptable. Review should receive final sign-off by 1.10.2012*
  - f. Microbiology: *Review in darrts*
  - g. Statistics: *Review should receive final sign-off by 1.6.2012*
  - h. DRISK: *Tertiary review is needed and should receive final sign-off as soon as clinical and nonclinical review finalized and signed off.*
  - i. DMEPA: *Review in darrts*
  - j. DDMAC: *Review in darrts*
  - k. DSI: *Review in darrts*
  - l. Facilities: *The EER should be completed prior to January 20, 2012*
4. PMR Status:
- a. Nonclinical: *PMR's proposed are acceptable. PMR template will be uploaded soon.*
  - b. Clinical Pharmacology: *Language on proposed PMR is close to completion. As soon as data analysis for above mentioned draft PMR is received and reviewed, PMR templates will be uploaded.*
  - c. Clinical: *Will be finalized after review of GNE's 1.5.2012 submission. PMR template will be uploaded soon*
5. Labeling Status: *Genentech response to FDA proposed changes dated 12.14.11 was received on 12.21.11. How/when would team like to review Genentech's responses? Should the internal team meeting scheduled for January 11, 2012 be used for this? Will review GNE's response at next team meeting scheduled for 1.11.2012*
6. Proposed Action: *FDA seeking Approval action*
7. Postmarket Safety Surveillance Plan: *Clinical team conveyed adverse events that could be seen post-marketing.*
8. FDA Outreach:
- a. Information Advisory to DHHS
  - b. FDA press release
  - c. ASCO Burst

Discussion: *Erika Jefferson and Ginneh Stowe will be notified of DOP2's desire to issue press release and ASCO Burst*

9. Miscellaneous:

- a. *Postfeedback meeting offered to sponsor. Genentech has tentatively accepted request. RPM will schedule.*

The meeting concludes.

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MONA G PATEL  
01/12/2012

**REQUEST FOR DDMAC LABELING REVIEW CONSULTATION**

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) Mona Patel RPM/DOP2; 301-796-4236 DOP2/OHOP/OODP/OND/CDER/FDA
------------------------------	---

REQUEST DATE January 5, 2012	IND NO.	NDA/BLA NO. 20388/26	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Amendment to original NDA/Pharmacovigilance Program
---------------------------------	---------	-------------------------	--

NAME OF DRUG vismodegib (ERIVEDGE)	PRIORITY CONSIDERATION Priority Review (6 months)	CLASSIFICATION OF DRUG Oncology (Small Molecule)	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) ASAP
---------------------------------------	--	---	--

NAME OF FIRM: Genentech, Inc.	PDUFA Date: March 8, 2012 (targeted 2.3.2012)
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**TYPE OF LABEL TO REVIEW**

<b>TYPE OF LABELING:</b> (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input 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	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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**EDR link to submission:**

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. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Please review/provide comment on the DHCP letter sent to us on 1.5.2012 in response to 12.13.11 telecon requesting revised risk management proposal.

- DRAFT "Now Approved" letter for HCPs provided in Word format for FDA comment

SIGNATURE OF REQUESTER  
Mona Patel

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

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MONA G PATEL  
01/06/2012

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Labeling Meeting  
1-5-12**

Memorandum

**Date:** January 5, 2012

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Labeling Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]

**Submission Date:** September 8, 2011

**Received Date:** September 8, 2011

**Sponsor:** Genentech, Incorporated

**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

Attendees:

Patricia Keegan

Mona Patel

Jeff Summers

Michael Axelson

Carole Broadnax

Karen Munoz

Sharon Mills

Medication Guide was discussed. Team will finalize offline.

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MONA G PATEL  
01/06/2012

**From:** Patel, Mona  
**Sent:** Tuesday, January 03, 2012 5:43 PM  
**To:** 'Sarah Wayson'  
**Subject:** RE: NDA 203388 Vismodegib: clinical pharmacology PMRs  
Sarah,

We believe we may be able to take an earlier action than the PDUFA date and we are targeting Friday February 3, 2012 for taking action. We would appreciate receiving responses from your team sooner than what is proposed below.

Mona

---

**From:** Sarah Wayson [mailto:wayson.sarah@gene.com]  
**Sent:** Tuesday, January 03, 2012 3:36 PM  
**To:** Patel, Mona  
**Subject:** Re: NDA 203388 Vismodegib: clinical pharmacology PMRs

Dear Mona,

Happy New Year! I just wanted to give you a quick update on this week's activities on the Genentech side:

- Our response from the December 13 telecon to discuss the risk management strategy is on track so I plan to email that to you tonight with the formal submission to follow tomorrow. In this response we will be providing the details of our (b) (4) draft PMR language that will hopefully address all of FDA's concerns and enable us to close-out this component.

- Regarding the PMRs you forwarded Friday, December 30, the team would like to propose a data analysis alternative to the requested study to evaluate the effects of H2 antagonists, proton pump inhibitors and antacids. I intend to submit our response to you via email before 5PM EST tomorrow (Wed 1/4). If the proposal is considered acceptable, we would be able to provide the data analysis by Friday, January 13.

I will probably be out-of-the-office next Monday, Jan 9, but I will check email regularly and can be reached on my corporate mobile at 650-238-8736.

Hope you are doing well!

Best,  
Sarah

Sarah Wayson, PhD | Scientist, Product Development Regulatory - Program Management | Genentech, Inc., A Member of the Roche Group | desk: 650-225-7928 | mobile: 650-238-8736

On Fri, Dec 30, 2011 at 7:11 AM, Patel, Mona <[Mona.Patel@fda.hhs.gov](mailto:Mona.Patel@fda.hhs.gov)> wrote:

- To conduct a clinical trial according to “FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function -Study Design, Data Analysis and Impact on Dosing and Labeling” The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The organ dysfunction groups should be balanced with respect to age, gender and weight. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

The timetable you submitted on 10.17.11 states that you will conduct this trial according to the following schedule:

Draft Protocol Submitted to the FDA: 3 October 2011, Serial Number 0248  
Final Protocol Submission Date: (b) (4)  
Trial Completion Date: September 2014  
Final Report Submission: March 2015

- To conduct a clinical trial according to “FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling”. A "reduced" renal impairment study could be proposed to include subjects with normal renal function and subjects with severe renal impairment. The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The organ dysfunction groups should be balanced with respect to age, gender and weight. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

The timetable you submitted on 10.17.11 states that you will conduct this trial according to the following schedule:

Draft Protocol Submitted to the FDA: 3 October 2011, Serial Number 0248  
Final Protocol Submission Date: (b) (4)  
Trial Completion Date: September 2014  
Final Report Submission: March 2015

- To submit a final report for the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (rosiglitazone) and on the

pharmacokinetics of oral contraceptive components (ethinyl estradiol and norethindrone).

The timetable you submitted on 10.17.11 states that you will conduct this trial according to the following schedule:

Trial Completion Date: March 2012

Final Report Submission: March 2012

- To conduct a clinical trial to evaluate if H<sub>2</sub> antagonists, proton pump inhibitors and antacids alter the bioavailability of vismodegib. The study results should allow for a determination on how to dose vismodegib with regard to these gastric pH elevating agents.

Please submit the timeline as indicated below.

Final Protocol Submission Date:

Trial Completion Date:

Final Report Submission:

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MONA G PATEL  
01/31/2012

**From:** Patel, Mona  
**Sent:** Friday, December 30, 2011 10:12 AM  
**To:** 'Sarah Wayson'  
**Subject:** NDA 203388 Vismodegib: clinical pharmacology PMRs

**Importance:** High

- To conduct a clinical trial according to “FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function -Study Design, Data Analysis and Impact on Dosing and Labeling” The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The organ dysfunction groups should be balanced with respect to age, gender and weight. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

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Final Protocol Submission Date: January 2012  
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Final Report Submission: March 2015

- To conduct a clinical trial according to “FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling”. A "reduced" renal impairment study could be proposed to include subjects with normal renal function and subjects with severe renal impairment. The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The organ dysfunction groups should be balanced with respect to age, gender and weight. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

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Final Protocol Submission Date: January 2012  
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Final Report Submission: March 2015

- To submit a final report for the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (rosiglitazone) and on the pharmacokinetics of oral contraceptive components (ethinyl estradiol and norethindrone).

The timetable you submitted on 10.17.11 states that you will conduct this trial according to the following schedule:

Trial Completion Date: March 2012  
Final Report Submission: March 2012

- To conduct a clinical trial to evaluate if H<sub>2</sub> antagonists, proton pump inhibitors and antacids alter the bioavailability of vismodegib. The study results should allow for a determination on how to dose vismodegib with regard to these gastric pH elevating agents.

Please submit the timeline as indicated below.

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

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/s/  
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MONA G PATEL  
12/30/2011



NDA 203388

**INFORMATION REQUEST**

Genentech, Inc.  
Attention: Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your New Drug Application (NDA) submitted and received September 8, 2011, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for vismodegib capsules, 150 mg.

We also refer to your amendments dated October 17, 2011, November 23, 2011, and November 29, 2011.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response no later than December 28, 2011, in order to continue our evaluation of your NDA.



(b) (4)

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

Sincerely,

*{See appended electronic signature page}*

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

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SARAH P MIKSINSKI  
12/19/2011

**From:** Patel, Mona  
**Sent:** Friday, December 16, 2011 12:07 PM  
**To:** 'Sarah Wayson'  
**Subject:** Please propose timelines: Nonclinical PMR's (NDA 203388)

Sarah,

Please propose timelines for each PMR noted below. We would appreciate a response (via email) by 8am EST, Friday, December 23, 2011. Once we have sent you all the PMR's to respond to (checking with clin.pharm and clinical) and we have finalized the agreed upon language and timelines, you may submit formally 1 submission containing all of the internal discourse summarized comprehensively. Also, as was communicated in an email to Wen Liu earlier in the review, please keep in mind that proposed PMR's submitted should be presented to us in a manner one may find in an action letter which will always include dates for Final Protocol Submission, Trial/study completion, and Final Report Submission. We may add other milestone dates for you to consider too. With regards to the Final Report Submission date, it should be understood that the protocol should be final in regards to meeting the goals of the PMR at that milestone due date and therefore we recommend that Genentech submit the "final" protocol 60 days in advance of that date so FDA can review the protocol and identify any deficiencies that need to be addressed before the final protocol due date established. Please be sure the dates you propose allow time for you to submit protocol ahead of milestone for FDA to review and provide feedback for you to consider in submitting the final protocol.

1. To evaluate the potential for a serious risk of carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study. The SPA for the carcinogenicity study in the mouse will be submitted by WWWW, 201W, the final protocol will be submitted by XXXX, 201X, the study will be completed by YYYY, 201Y, and the final study reports submitted by ZZZZ, 201Z.
2. To evaluate the potential for a serious risk of carcinogenicity, conduct a long-term (2 year) rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study. The SPA for the carcinogenicity study in the rat will be submitted by WWWW, 201W, the final protocol will be submitted by XXXX, 201X, the study will be completed by YYYY, 201Y, and the final study reports submitted by ZZZZ, 201Z.

Please ack receipt.

Mona

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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/s/  
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MONA G PATEL  
12/16/2011



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

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Telecon Minutes

**Date:** December 15, 2011

**From:** Mona Patel, Pharm.D., DBOP/OODP/OND/CDER/FDA

**Subject:** December 13, 2011 Telecon w/ Genentech

**Product:** vismodegib (NDA 20338); proposed indication “for treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)”

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Purpose: FDA requested this teleconference with Genentech to discuss the revised risk management strategy submitted on November 4, 2011.

Background: On September 11, 2011, Genentech submitted NDA 203388 for vismodegib, [REDACTED] (b) (4). On October 20, 2011, FDA held a telecon with Genentech to discuss Genentech’s proposed [REDACTED] (b) (4) submitted with the September 8, 2011 new NDA. At the conclusion of the October 20, 2011 telecon, it was agreed that Genentech would submit a revised risk management strategy in communicating the potential risks of embryo-fetal toxicities associated with vismodegib and would describe in detail the specific objectives or goals. Genentech submitted their revised risk management proposal on November 4, 2011 with accompanying draft supporting materials submitted on November 18, 2011.

---

FDA Attendees:

Mona Patel, Pharm.D., Regulatory Health Project Manager, OHOP/DOP2  
Jeff Summers, M.D., Deputy Director of Safety, OHOP/DOP2  
Patricia Keegan, M.D., Director, OHOP/DOP2  
Michael Axelson, M.D., Clinical Reviewer, OHOP/DOP2  
Ke Liu, M.D., Clinical Team Leader, OHOP/DOP2  
Todd Palmby, Ph.D., Acting Supervisory Toxicologist, OHOP/DHOT  
Dubravka Kufirin, Ph.D., Toxicologist, OHOP/DHOT  
Amarilys Vega, M.D., M.P.H, Reviewer, OSE/DRISK  
Cynthia LaCivita, Pharm.D., Team Leader, OSE/DRISK  
Tammie B Howard, RN, MSN, Maternal Health Reviewer, MHT  
Sharon Mills, Ph.D., Patient Labeling Reviewer, OSE/OMEPRM/DRISK  
Melissa Tassinari, Ph.D., Acting Team Leader, MHT

Robert Pratt, Pharm.D. Team Leader Safety Evaluator, OSE/DPV2

Genentech Attendees:

Sarah Wayson, Ph.D., Regulatory US Partner for vismodegib, Product Development Regulatory

Jennifer Low, M.D., Ph.D. Global Development Team Lead for vismodegib & Group Medical Director, Product Development Oncology (she will be the primary speaker)

Virginia Bryan, Associate Director, US Commercial Regulatory Affairs

Richard Graham, Ph.D., Clinical Pharmacology and Nonclinical Team Lead

Joseph H. Hoffman, M.D., F.C.C.P., Global Head, Safety Science Oncology, Safety Risk Management

Wen Liu, Ph.D., vismodegib Global Regulatory Lead, Product Development Regulatory

Howard Mackey, Ph.D. Senior Statistical Scientist, Product Development

Eric Morinello, Ph.D., DABT Toxicology Scientist, Safety Assessment Toxicology

Josina Reddy, M.D., Ph.D., Senior Medical Director, Product Development Oncology

Michelle Rohrer, Ph.D. Vice President, US Product Development Regulatory

Maria D. Tello, M.D., Oncology Safety Scientist, Product Development Safety

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FDA initiated the discussion, responding to Genentech's November 30, 2011 request for advice on submission of a new proprietary name request, in case the European Medicines Agency (EMA) did not grant the proprietary name of ERIVEDGE. FDA recommended that Genentech hold off on submitting a new proprietary name request until the EMA responds to Genentech since doing so would result in withdrawal of the prior tradename approval, while the new tradename review would be subject to a 90-day review.

FDA also responded to Genentech's inquiry from December 12, 2011 regarding the FDA's request on December 9, 2011

(b) (4)

FDA then discussed the November 4 and November 18, 2011 submissions containing Genentech's revised risk management strategy. FDA requested more detail on the proposed "enhanced pharmacovigilance" program for pregnancy and inquired whether Genentech has considered a pregnancy registry for this drug. Genentech stated that a pregnancy registry could be developed for this drug, however the number of pregnant women enrolled in the pregnancy registry would probably be too low to provide useful information and therefore favored a surveillance program. FDA requested clarification on asked how healthcare providers would be made aware of the existence of a pregnancy registry, how Genentech would ensure the completeness of reporting of pregnancy outcomes (encourage patient enrollment and physician participation), and how the program might differ from the pregnancy registry for Herceptin, based on Genentech's experience with this program. Genentech noted that the pregnancy registry for Herceptin

was designed through the guidance of FDA. Genentech stated that even though a pregnancy registry could be useful in collecting specified data, there are challenges associated with the data collected due to the low numbers. Genentech agreed to submit sample case report forms for data collection to FDA for review.

FDA informed Genentech that a postmarketing requirement (PMR) on the enhanced pregnancy surveillance and reporting would be necessary to support approval of vismodegib and asked Genentech to submit PMR language along with milestones for FDA to review. FDA also informed Genentech when they set up the milestones, sufficient lead-time should be allotted for FDA review and feedback and submission of revised plans so that the milestones for final, agreed-upon documents can be met. FDA also informed Genentech that reports for PMRs should be submitted as stand-alone submissions (one submission per PMR report) with a clear title on the cover letter outlining the purpose of the submission, i.e., Interim report for enhanced pregnancy surveillance program. PMR reports should not be included in periodic safety update reports (PSUR). FDA also asked Genentech to edit the supporting materials to remove redundant information and to send word documents of the communication tools to allow FDA to provide edits and comments.

FDA requested that Genentech submit a proposal for FDA to review by 3 pm Wednesday, December 21, 2011. Genentech responded that they attempt to meet this deadline, but could not guarantee that they would be able to provide all the necessary materials for FDA to review by the requested date. FDA noted.

Call concluded.

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/s/  
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MONA G PATEL  
12/20/2011

## Patel, Mona

---

**From:** Patel, Mona  
**Sent:** Wednesday, December 14, 2011 9:27 AM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Proposed Changes to Vismodegib USPI (NDA 203388)

**Attachments:** FDA Proposed Vismodegib (NDA 203388) Labeling (12 14 11).doc

Sarah,

Attached are the FDA proposed changes to the USPI for vismodegib under NDA 203388. We would appreciate receiving a response back by 12pm EST, Wednesday, December 21, 2011.

As Dr. Keegan mentioned to you yesterday, these changes are only for the USPI at this time. Comments will be forthcoming on the Medication Guide sometime the first week in January. Also, we started making changes to the highlights, but we usually refrain from editing until the labeling negotiations become final to ensure language is consistent.

Please ack receipt.

Mona



FDA Proposed  
/ismodegib (NDA 2..

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993  
☎ 301.796.4236 (phone) • 301.796.9849 (fax) | mona.patel@fda.hhs.gov (email)



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

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/s/  
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MONA G PATEL  
12/14/2011

**eCTD NDA 203388/0**  
**vismodegib (Erivedge)**  
**Internal Team Meeting**  
**12-5-11**

Memorandum

**Date:** December 12, 2011

**From:** Mona Patel, DOP2/OODP/CDER

**Subject:** Internal Team Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

**Attendees:**

Patricia Keegan  
Mona Patel  
Jeff Summers  
Ke Liu  
Michael Axelson  
Amarilys Vega  
Cynthia LaCivita  
Todd Palmby  
Dubravaka Kufrin  
Tammie B. Howard  
Melissa Tassinari

This internal meeting was held to discuss outcome of December 9, 2011 Regulatory Briefing on 'Risk Mitigation Strategies for Teratogenicity for vismodegib, a hedgehog pathway' and to prepare for December 13, 2011 teleconference with Genentech, Incorporated.

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/s/  
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MONA G PATEL  
12/12/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Labeling Meeting  
12-12-11**

Memorandum

**Date:** December 12, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Labeling Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

Attendees:

Patricia Keegan

Mona Patel

Jeff Summers

Janice Brown

Zedong Dong

Ke Liu

Michael Axelson

Todd Palmby

Dubravaka Kufrin

Tammie B. Howard

Melissa Tassinari

Section 8 (Use in Specific Populations), Section 5 (Warnings and Precautions), and Section 16 (How Supplied/Storage and Handling) was discussed. Team will finalize offline.

Section 17 (Patient Counseling Information) was discussed and finished.

Section 11 (Description) was discussed and revised. Team will finalize offline.

[REDACTED] (b) (4)

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/s/  
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MONA G PATEL  
12/12/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Labeling Meeting  
12-9-11**

Memorandum

**Date:** December 9, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Labeling Meeting: NDA 203388

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**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]

**Submission Date:** September 8, 2011

**Received Date:** September 8, 2011

**Sponsor:** Genentech, Incorporated

**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

Section 14 (Clinical Studies) was discussed and finished.

DMEPA/CMC comments to Carton and Container labeling were discussed.

DDMAC had no comments to Carton and Container labeling.

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/s/  
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MONA G PATEL  
12/09/2011

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From: Patel, Mona  
Sent: Friday, December 09, 2011 10:22 AM  
To: 'Sarah Wayson'  
Subject: Quality Assessment Form-NDA 203388

Sarah,

Attached is the QA form for your internal use and if you should desire a postfeedback meeting with us for NDA 203388.

Do you think a postfeedback meeting is something your team might like to have after we take action? If so, please let me know no later than January 13, 2012 as calendars here book up pretty fast, and if you should desire one, we would like to hold it in a timely fashion.

Mona

## **Quality Assessment for NDA/BLA Submissions**

**Purpose:** This assessment is intended to be used by both the applicant and members of CDER's review team. It is designed to guide them through the pertinent sections of an application and to assist in assessing the content of the NDA/BLA submission as well as the overall review process. It is to be used to record information solely to facilitate discussion of lessons learned at the post-action feedback meeting of both parties. It is to play no role in the FDA action taken on an application and is not to be used in dispute resolution. It will not be archived with the application by FDA.

**When to Use:** At this time, CDER will offer this assessment and the post-action feedback meeting for all NMEs and original BLAs; CDER may offer these for other applications and supplements. The Quality Assessment form should be distributed to each of the review team members, as well as to the applicant, at the pre-NDA/BLA meeting with an explanation of how it will be used. If a pre-NDA/BLA meeting is not held, this assessment should be provided to the applicant via email. Both the applicant and review team members are encouraged to periodically add information to their Quality Assessment form during the review process. This assessment should be used to guide post-action feedback meetings between the FDA and the application.

### **Instructions for Completing the Quality Assessment**

**FDA:** This assessment is to be filled out during the review cycle by individual reviewers as issues relating to the review and application arise. It should be completed by the end of the review and used during the post-action feedback meetings with the applicant. Reviewers should capture as much additional information as possible on the last page of the assessment.

**Applicant:** This assessment should be filled out both while preparing the submission and during the review cycle. You can use it to record your experience with the review process, including the steps preceding submission of the BLA/NDA.

**The Post-Action Feedback Meeting:** This assessment will be used in the post-action feedback meeting only as a guide for the discussion. The applicant and all CDER reviewers should bring their completed assessment and use it as a reference for issues that are pertinent to the discussion. Due to the sizable content of the assessment, it is not expected that every question be discussed. The meeting should focus on those items that provide lessons learned (i.e., things that worked well and things that did not) for future applications.

**Collection and Archiving:** This assessment is not to be collected and it is not to be archived. It is for the applicant and each CDER reviewer to retain and dispose of at their discretion.



### Quality Assessment for NDA/BLA Submissions

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	(If electronic submission) Proper eCTD lifecycle XML relationships were established in all submissions.	
	(If electronic submission) All hyperlinks in the application worked appropriately.	
	The application included: <ul style="list-style-type: none"> <li>• Required forms appropriately completed</li> <li>• Information requested by FDA during pre-submission drug development <b>and</b> per applicable guidance and regulations</li> </ul>	
	The application appropriately reflected previous advice and requests from FDA (e.g., regarding development program, study design and endpoints, GCP issues and analysis of results, CMC issues) or included reasonable justification for all deviations from FDA guidance or pre-submission advice.	
<b>Summaries/ Overviews</b>	The summaries highlighted the important issues.	
	The summaries accurately reflected supporting data, including appropriate links.	
<b>Technical Sections</b>	Datasets were complete and in a format to facilitate FDA analysis.	
	Appropriate analyses were performed by the applicant to evaluate efficacy, safety, and product quality, e.g., claims were based on pre-specified endpoints and analyses; any deviations justified; conformed to ICH and other guidelines.	
<b>Site Inspections</b>	Facilities were available for inspection upon application submission.	
	Facility inspections were completed in a timely manner.	
	Clinical site inspections were completed in a timely manner.	

### Quality Assessment for NDA/BLA Submissions

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	All deviations from GCP were identified for each clinical site in the initial submission and impact of deviations were discussed in the application.	
<b>Post-marketing Requirements (PMR) and Commitments (PMC)</b>	PMRs and PMCs, with timelines, conforming to ICH guidelines were included in the initial submission. Examples include PREA studies, confirmatory studies for accelerated approval, studies to evaluate previously identified safety issues.	
	If the need for PMRs or PMCs was identified by FDA during application review, discussion of postmarketing study proposals and timelines followed GRMP timelines.	
<b>Risk Evaluation and Mitigation Strategy (REMS)</b>	REMS, as discussed during pre-submission meeting, were included in the initial submission.	
	If a need for REMS was identified by FDA during application review, request for/discussion of REMS followed GRMP timelines.	
	FDA provided rationale for modifications to applicant's REMS.	
	Applicant followed FDA Guidance regarding content/organization of REMS.	
<b>Labeling</b>	Labeling contained annotations and/or hyperlinks to the location of supporting data in the application.	
	All references in proposed labeling were included in the submission.	
	Applicant followed FDA Guidance regarding content/organization of labeling, including patient labeling or Medication Guide and carton/container labeling.	
	FDA provided rationale for substantive modifications to applicant's labeling and FDA proposed changes were consistent with Guidances/policy.	
	FDA and applicant followed GRMP timelines for labeling discussions.	

### Quality Assessment for NDA/BLA Submissions

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	Applicant's submission of proprietary name review request followed FDA guidance (e.g., more than on proposed name). If submitted during the IND review, did this "add value" to proprietary name review? If not, why not?	
<b>Communi- cation</b>	FDA requests for information were clearly stated and reflected understanding of application contents.	
	The applicant responded to information requests raised during the review in a <i>timely</i> manner, including: <ul style="list-style-type: none"> <li>• Information requests during first 60 days</li> <li>• Day-74 letter</li> <li>• Information requests after 60 days</li> <li>• Discipline Review letters</li> </ul>	
	Applicant responded to issues raised during the review in a <i>complete</i> manner, i.e., no follow-up was required.	
	Did application contain information requested during IND review? Were there deficiencies communicated by FDA during the review (e.g., day 74, etc.) that should have been anticipated based on FDA comments prior to submission of the application?	
	Could issues raised by FDA during application review have been identified by FDA or applicant prior to submission?	
	How might communication or discussion of information requests been more efficient?	
	Significant deviations from the milestone timeline by FDA were communicated to the applicant.	

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/s/  
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MONA G PATEL  
12/09/2011

**From:** Patel, Mona  
**Sent:** Friday, December 09, 2011 4:30 PM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Comments to vismodegib carton/container (NDA 203388)

Sarah,

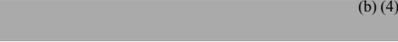
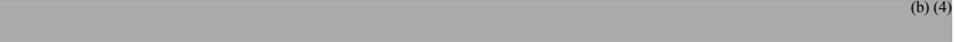
FDA has the following requests for changes to the carton and container labeling submitted in the September 8, 2011 submission under NDA 203388 for vismodegib. We are requesting revised labels be sent back to us via email by 4:30pm EST Friday, December 16, 2011. Once we have an agreed upon carton and container, we will then request for you to submit formally.

Please ack receipt.

### Container Labeling

1. Add a medication guide statement similar to the one included on the carton labeling to the principal display panel. The medication guide statement is required per 21 CFR 208.24(d).
2. Delete  (b) (4)
3. Include a usual dosage statement, "Usual Dosage: See prescribing information." on the side panel as required per 21 CFR 201.55. Place the statement underneath the "each capsule contains" statement above the storage instructions, if space permits.
4. Please add "Manufactured by Patheon, Inc., Mississauga, Canada" between the two lines "Made in Canada" and "Distributed by:"

### Carton Labeling

1. Relocate the medication guide statement to the principal display panel as it lacks prominence as required per 21 CFR 208.24(d).
2. Delete the  (b) (4)
3. Delete the  (b) (4)  
or  
replace it with an image of the actual Erivedge capsule.
4. Please add "Manufactured by Patheon, Inc., Mississauga, Canada" between the two lines "Made in Canada" and "Distributed by:"

Mona

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office

of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903  
New Hampshire Avenue | Silver Spring, MD 20993  
 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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MONA G PATEL  
12/09/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
12-5-11**

Memorandum

**Date:** December 5, 2011

**From:** Mona Patel, DBOP/OODP/CDER

**Subject:** Internal Team Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]

**Submission Date:** September 8, 2011

**Received Date:** September 8, 2011

**Sponsor:** Genentech, Incorporated

**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This internal meeting was held to review remaining timelines for application and to receive updates on reviews from each discipline.

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MONA G PATEL  
12/08/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Labeling Meeting  
12-2-11**

Memorandum

**Date:** December 2, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Labeling Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]

**Submission Date:** September 8, 2011

**Received Date:** September 8, 2011

**Sponsor:** Genentech, Incorporated

**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

Section 8 (Use in Specific Populations) (subsection 8.5, 8.6 and 8.7), Section 12 (Clinical Pharmacology), and Section 1 (Indications and usage) were discussed and completed.

Section 14 (Clinical Studies) were discussed and will be finished at December 9, 2011 labeling meetings.

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/s/

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MONA G PATEL  
12/08/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
12-1-11**

Memorandum

**Date:** December 1, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Practice Session for Regulatory Briefing: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This meeting was held to practice for December 9, 2011 regulatory briefing on pregnancy labeling [REDACTED] (b) (4) for vismodegib, a hedgehog pathway inhibitor.

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MONA G PATEL  
12/02/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Labeling Meeting  
11-30-11**

Memorandum

**Date:** November 30, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Labeling Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]

**Submission Date:** September 8, 2011

**Received Date:** September 8, 2011

**Sponsor:** Genentech, Incorporated

**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

Section 4 (Contraindications), Section 6 (Adverse Reactions), Section 10 (Overdosage), Section 13 (Nonclinical Toxicology), and Boxed Warning were discussed and completed.

Section 5 (Warnings & Precautions), Section 8 (Use In Specific Populations), and Section 17 (Patient Counseling Information) were discussed and will be re-visited at December 12, 2011 labeling meeting.

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MONA G PATEL  
11/30/2011

**From:** Patel, Mona  
**Sent:** Wednesday, November 30, 2011 3:11 PM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Request: Vismodegib Info request: NDA 203388

**Importance:** High  
Sarah,

From our clinical pharmacology team.

To GNE:

1. Among the 15 patients (Table 1) who had AEs leading to drug discontinuation, we are able to identify that 7 patients concomitantly received P-gp inhibitors. It's not clear whether the other 8 patients had received P-gp inhibitors or not. Please clarify.

2. Please provide the vismodegib total and free concentrations or any available PK parameter estimates for these 15 patients listed in the table. Please provide the data without and with P-gp inhibitor for intra-patient comparison, if available.

3. Please clarify whether those patients listed in Page 34-90 in your Listing A4 titled "All Adverse Events: Pooled Safety Population submitted on November 28, 2011, were exposed to P-gp inhibitors.

4. Please provide table(s) listing the vismodegib total and free concentrations or any available PK parameter estimates for the patients included in Figure 1 and 2 submitted on November 28, 2011.

**Table 1: Adverse Events Leading to Discontinuation**

<b>Trial</b>	<b>Subject</b>	<b>P-gp inhibitor</b>
3925	13116	Yes
4437	13005	Yes
4476	20507	Yes
	20540	Yes
	20545	Yes
	20562	Unknown
	20585	Unknown
	20600	Unknown
	20680	Unknown
	20681	Yes
	20720	Unknown
	20820	Yes
	20880	Unknown
	20924	Unknown
	21080	Unknown

Please provide your response by COB Friday, December 2, 2011.

Mona

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/s/  
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MONA G PATEL  
11/30/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
11-29-11**

Memorandum

**Date:** November 29, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Practice Session for Regulatory Briefing: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This meeting was held to practice for December 9, 2011 regulatory briefing on pregnancy labeling [REDACTED] (b) (4) for vismodegib, a hedgehog pathway inhibitor.

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/s/  
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MONA G PATEL  
11/30/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Labeling Meeting  
11-29-11**

Memorandum

**Date:** November 29, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Labeling Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge]

**Submission Date:** September 8, 2011

**Received Date:** September 8, 2011

**Sponsor:** Genentech, Incorporated

**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b)(4).

Section 2 (Dosage and Administration), Section 3 (Dosage Forms and Strengths), Section 11 (Description), and Section 16 (How Supplied/Storage and Handling) were discussed and completed.

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/s/  
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MONA G PATEL  
11/30/2011



IND 074573  
NDA 203388

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Genentech, Inc.  
1 DNA Way, MS#241B  
South San Francisco, California 94080-4990

ATTENTION: Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs

Dear Dr. Rohrer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act; and to your New Drug Application (NDA) dated September 8, 2011, received September 8, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vismodegib Capsules, 150 mg.

We also refer to your August 2, 2011, IND correspondence, received August 3, 2011; and to your September 8, 2011, NDA correspondence, received September 8, 2011, requesting review of the proposed proprietary name, Erivedge. We have completed our review of the proposed proprietary name, Erivedge, and have concluded that it is acceptable.

The proposed proprietary name, Erivedge, 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 September 8, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Mona Patel at (301)-796-4236.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
11/28/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Mid-Cycle Meeting  
11-21-11**

Memorandum

**Date:** November 21, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Mid-Cycle: NDA 203388

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**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Proposed Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

The following individuals gave a presentation on their review findings.

Mona Patel-Regulatory history  
Michael Axelson-Clinical  
Janet Jiang-Statistical  
Jian Wang-Clinical Pharmacology  
Zedong Dong-CMC  
Dubravaka Kufrin-Nonclinical  
Amarilys-REMS

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/s/  
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MONA G PATEL  
11/21/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
11-18-11**

Memorandum

**Date:** November 18, 2011

**From:** Mona Patel, DOP2/OHOP/CDER

**Subject:** Practice Session for Regulatory Briefing: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This meeting was held to practice for December 9, 2011 regulatory briefing on pregnancy labeling [REDACTED] (b) (4) for vismodegib, a hedgehog pathway inhibitor.

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MONA G PATEL  
11/21/2011



NDA 203388

**FILING COMMUNICATION**

Genentech, Inc.  
Attention: Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Rohrer:

Please refer to your New Drug Application (NDA) dated September 8, 2011, received September 8, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for vismodegib, capsules 150 mg.

During our filing review of your application, we identified the following potential labeling review issues:

**General Comments**

1. Use command language throughout labeling.

**Highlights**

2. The drug proper name following the tradename in the Highlights heading should be in parentheses and not brackets, e.g. Tradename (vismodegib).
3. Each summarized statement under the appropriate Highlights heading must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information (i.e. DOSAGE AND ADMINISTRATION statement should reference section 2 of FPI).
4. The amount of white space is not consistent between sections in Highlights, e.g. white space should be decreased before USE IN SPECIFIC POPULATIONS.
5. All headings should be presented in the center of a horizontal line.

(b) (4)

7. Contact information (name, telephone number, and web address) needs to be added for reporting suspected adverse reactions.

**Table of Contents**

8. The same title for the boxed warning should appear in the HL, FPI and TOC.

9. The statement [REDACTED] (b) (4) should read as “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information**

10. Identifying numbers should be presented in bold print and should precede the heading or subheading by at least two squares the size of the letter “m” in 8 point type. Specifically, spacing needs to be adjusted for section and subheadings under section 12 and 13.

(b) (4)

13. In the Boxed Warning, subsection 5.1 is not cross-referenced. Please clarify why this section is not cross-referenced.
14. A bullet should be used for each contraindication rather than subsections.
15. In section 6.1, paragraph 1, line 3, please add the word “clinical” before the word “practice.”
16. If data do not support a pediatric indication, the following statement: “Safety and effectiveness have not been established in pediatric patients” should be added in subsection 8.4.
17. In section 16, the units in which the dosage form is ordinarily available for prescribing by practitioners should be stated (e.g., bottles of #).
18. The statement “See FDA-approved patient labeling (Medication Guide)” should appear at the beginning of Section 17 to give it prominence.
19. Please clarify why the manufacturer name and address information is not identical between FPI and MG.
20. The revision date at the end of Highlights replaces the [REDACTED] (b) (4) date at the end of the full prescribing information and should not appear in both places. [REDACTED] (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you resubmit labeling that addresses these issues by November 23, 2011. The resubmitted labeling will be used for further labeling discussions.

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

### **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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Dr. Mona Patel, Regulatory Project Manager, at (301) 796-4236.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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PATRICIA KEEGAN  
11/17/2011

**From:** Patel, Mona  
**Sent:** Wednesday, November 16, 2011 3:15 PM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Request For Information: Clinical Pharmacology NDA 203388

Sarah,

Our clinical pharmacology team has the below information request for NDA 203388. Please provide a response via email by 3pm Wednesday, November 23, 2011 and follow up with formal submission.

Mona

Since vismodegib is a P-gp substrate based on your *in vitro* screening, please performed an exploratory analysis of the effect of P-gp inhibitors on vismodegib systemic exposure, efficacy and safety. This analysis should compare the systemic exposure of vismodegib, efficacy and safety between patients who did not received P-gp inhibitors and patients who concomitantly received any P-gp inhibitors such as Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil. Please submit the analysis results together with the line listing individual data for FDA review and determination of the necessity of any further studies.

Please ack. receipt.

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Oncology Products, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

☎ 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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/s/  
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MONA G PATEL  
11/16/2011



NDA 203388

**INFORMATION REQUEST**

Genentech, Inc.  
Attention: Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your New Drug Application (NDA) submitted and received September 8, 2011, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for vismodegib capsules, 150 mg.

We also refer to your amendment submitted October 17, 2011, received October 18, 2011.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response no later than November 29, 2011, order to continue our evaluation of your NDA.

1. Provide the instrumental testing conditions for the dissolution profiles [REDACTED] (b) (4)
2. Provide the solubility of vismodegib [REDACTED] (b) (4)
3. Provide the stability dissolution mean profiles and the actual data for the individual test results in EXCEL or SAS format for the vismodegib drug product from the primary stability samples stored under long term conditions (1, 3, 6, 9, 12, and 18 months) as well as accelerated conditions (1, 3, and 6 months).
4. Provide the dissolution profile data (n=12, individual, mean, minimum and maximum, RSD) for the lots of vismodegib drug product [REDACTED] (b) (4) used in the clinical and PK studies.

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

Sincerely,

*{See appended electronic signature page}*

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

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SARAH P MIKSINSKI  
11/16/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
11-14-11**

Memorandum

**Date:** November 14, 2011

**From:** Mona Patel, DBOP/OODP/CDER

**Subject:** Internal Team Meeting: NDA 203388

---

**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This internal meeting was held to review slides for December 9, 2011 regulatory briefing on pregnancy labeling [REDACTED] (b) (4) for vismodegib, a hedgehog pathway inhibitor.

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MONA G PATEL  
11/16/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
11-4-11**

Memorandum

**Date:** November 4, 2011

**From:** Mona Patel, DBOP/OODP/CDER

**Subject:** Internal Team Meeting: NDA 203388

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**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This internal meeting was held to discuss logistics and content for a regulatory briefing on pregnancy labeling [REDACTED] (b) (4) for vismodegib, a hedgehog pathway inhibitor.

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MONA G PATEL  
11/16/2011



NDA 203388

**PRIORITY REVIEW DESIGNATION**

Genentech, Inc.  
Attention: Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Rohrer:

Please refer to your New Drug Application (NDA) dated September 8, 2011, received September 8, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for vismodegib, capsules 150 mg.

We also refer to your amendments received through November 3, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is March 8, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 16, 2012.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before November 21, 2011.

If you have any questions, call Dr. Mona Patel, Regulatory Project Manager, at (301) 796-4236.

Sincerely,

*{See appended electronic signature page}*

Patricia A. Keegan  
Division Director  
Division of Oncology Products 2  
Office of Hematology & Oncology Products  
Center for Drug Evaluation and Research

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PATRICIA KEEGAN  
11/04/2011



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

**Memorandum**

**DATE:** November 3, 2011

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

**SUBJECT:** Designation of NDA application review status  
Sponsor: Genentech, Incorporated  
Product: vismodegib (capsules)  
Indication: Treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b)(4).

**TO:** NDA 203388

The review status of this file submitted as a NDA application is designated to be:

Standard (10 Months)

Priority (6 Months)

Patricia Keegan, M.D.: \_\_\_\_\_

*{See appended electronic signature page}*

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MONA G PATEL  
11/03/2011

PATRICIA KEEGAN  
11/03/2011

**From:** Patel, Mona  
**Sent:** Tuesday, November 01, 2011 12:57 PM  
**To:** 'Sarah Wayson'  
**Subject:** Please Clarify: Genentech Response to October 5, 2011 IR & Outstanding Deficiencies: NDA 203388 (vismodegib)

**Importance:** High  
Sarah,

Based off your response to our 10.5.2011 IR, it appears that there is a mistake by GNE in the proposed PMR statement:

PMR #2:

Submit the final report from the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (i.e., rosiglitazone) and on the pharmacokinetics of oral contraceptive components (i.e., ethinyl estradiol and norethindrone). The study will be completed by 30 March 2012 (last patient out), and the final report will be submitted by 31 March 2012.

It can't be one day interval for the two timelines. Can you please clarify the timeline for this PMR (DDI)?

Thanks,  
Mona

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Biologic Oncology Products, Office of Oncology Drug Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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MONA G PATEL  
11/01/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
10-26-11**

Memorandum

**Date:** October 26, 2011

**From:** Mona Patel, DBOP/OODP/CDER

**Subject:** Internal Team Meeting: NDA 203388

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**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This internal meeting was held to discuss logistics and content for a regulatory briefing on pregnancy labeling [REDACTED] (b) (4) for vismodegib, a hedgehog pathway inhibitor.

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MONA G PATEL  
11/16/2011



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

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Telecon Minutes

**Date:** October 25, 2011

**From:** Mona Patel, Pharm.D., DBOP/OODP/OND/CDER/FDA

**Subject:** NDA 203388: Vismodegib October 20, 2011 Telecon w/ Genentech

**Product:** Vismodegib for treatment of adult patients with advanced basal cell carcinoma  
[REDACTED] (b) (4)

---

Purpose: FDA requested this telecon to seek clarity and gather information on Genentech's proposed [REDACTED] (b) (4) for vismodegib under NDA 203388.

---

FDA Attendees:

Mona Patel  
Jeff Summers  
Patricia Keegan  
Michael Axelson  
Ke Liu  
Todd Palmby  
Dubravaka Kufirin  
Amarilys Vega  
Cynthia Lacivita  
Tammie B Howard  
Karen Feibus  
Sharon Mills  
Melissa Tassinari  
John Leighton

Genentech Attendees:

Jennifer Low, Global Development Leader  
Michelle Rohrer, VP Regulatory  
Maryann Major, REMS specialist, Regulatory Program Manager  
Joseph Hoffman, Safety Cluster Head Oncology  
Sarah Wayson, Regulatory Program Manager

Wen Liu, Global Regulatory Lead  
Karen Jones, Head of Global Oncology Regulatory  
Virginie Bryan, REMS Specialist  
Josina Reddy, Medical Director  
Israel Gutierrez, Safety Science Lead  
Eric Morinello, Safety Toxicology  
Rick Graham, Clinical Pharmacology

The following discussion points were sent to Genentech on October 19, 2011 and discussed during the telecon on October 20, 2011.

The Division agrees that vismodegib has demonstrated teratogenic effects in animal studies and that such information be communicated to healthcare providers and patients to ensure safe use of vismodegib. The Division also believes that this would include, at minimum, communication of risks through accurate and detailed descriptions of the observations in labeling (i.e., physician product labeling and Medication Guide). These measures should include a Boxed Warning as well as information under the Warning and Precautions sections directed towards use of vismodegib among females and males of reproductive potential with locally advanced or metastatic basal cell carcinoma.

(b) (4)

(b) (4)

6. Please justify why vismodegib must be stopped in woman with positive pregnancy tests. Have you considered alternative actions that a positive pregnancy test should trigger - such as counseling with the prescribing physician and referral as appropriate (see also 8b)?

**Discussion:** Genentech stated they had considered vismodegib to be Pregnancy Category (b) (4) and therefore, placed the requirement in labeling to test female patients of child-bearing potential every month. FDA stated that vismodegib may not be considered as Pregnancy Category (b) (4) FDA also requested that Genentech re-consider the requirement for routine urine versus serum pregnancy tests.

7. Are you planning to do additional animal studies that would examine the effect of the drug in males and their offspring?

**Discussion:** Genentech stated they were not planning additional studies to examine the effects of the drug in males and their offsprings, but were planning to assess the level of vismodegib in semen from males in an ongoing or future clinical trial.

FDA requested that Genentech propose its approach(es) in communicating the potential risks of embryo-fetal toxicities associated with vismodegib and specific objectives or goals must be clearly described. Genentech acknowledged FDA's request and agreed to submit revised risk management programs within 3 weeks.

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/s/  
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MONA G PATEL  
11/22/2011

**From:** Patel, Mona  
**Sent:** Tuesday, October 25, 2011 9:24 AM  
**To:** 'Sarah Wayson'  
**Subject:** FDA Information Request: Pharmacometric

Sarah,

We have the following information request for NDA 203388. We are requesting a response by 12pm EST Thursday, October 27, 2011.

Please ack. receipt.

The submitted pharmacokinetics information for study SHH4476g show some inconsistencies between the reported data in the study report (csr-SHH4476g, pages 2225-2229) and the submitted PK datasets (adpc.xpt and pc.xpt). The study report shows Vismodegib total concentrations data is available for 78 patients, but the adpc.xpt and pc.xpt datasets show total Vismodegib concentration data is available for only 52 patients. Please submit updated PK datasets with the correct number of patients.

Mona

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Biologic Oncology Products, Office of Oncology Drug Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

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MONA G PATEL  
10/25/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
10-24-11**

Memorandum

**Date:** October 24, 2011

**From:** Mona Patel, DBOP/OODP/CDER

**Subject:** First Internal Team Meeting: NDA 203388

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**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This internal meeting was held to receive updates from review disciplines on outstanding deficiencies [REDACTED] (b) (4)

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/s/  
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MONA G PATEL  
11/16/2011



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

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Memo

**Date:** October 19, 2011

**From:** Mona Patel, Pharm.D., DBOP/OODP/OND/CDER/FDA

**Subject:** NDA 203388: Vismodegib REMS Discussion Points

**Product:** Vismodegib for treatment of adult patients with advanced basal cell carcinoma  
(b) (4)

**Meeting Date:** October 20, 2011, 12:00pm-1:00pm EST

---

The Division agrees that vismodegib has demonstrated teratogenic effects in animal studies and such information must be provided to healthcare providers and patients to ensure its safe use. The Division also believes that such a safe use must be appropriately done, at minimum, through thoughtful and thorough written labeling (i.e., physician product labeling and Medication Guide). These measures must include a Boxed Warning as well as information under the Warning and Precautions sections to facilitate a safe use of vismodegib among females and males of reproductive potential with locally advanced or metastatic basal cell carcinoma.

With respect to the need of REMS for vismodegib use, the Division is considering the following:

- The Division's review of recently approved oncologic drugs and biologics showed that REMS were not required for agents that had similar teratogenic effects as vismodegib in animal studies.
- If approved, the patient population is expected to be small. In addition, based on the NDA data submitted, median age of patients who received vismodegib was 61 year old, an age not commonly associated with patients who have reproductive potential.

(b) (4)

If you believe that a REMS is necessary to ensure vismodegib's safe use in addition to measures discussed above, please provide a rationale to do so. Specifically, please address the following issues:

1. Why are you proposing a different risk management strategy for vismodegib than other potential teratogens that you currently market (e.g., Herceptin)?
2. Is a REMS with ETASU needed to achieve both appropriate access and safe use?
3. If so, could this be done without creating unnecessary or cumbersome barriers to drug access for patients?
4. Who would ETASU benefit?
5. What additional value(s) does a REMS have that can not be accomplished with thoughtfully written labeling and MedGuide?
6. Please justify why drug should be stopped for any woman with a positive pregnancy test or have you considered alternative actions that a positive pregnancy test should trigger - such as counseling with the prescribing physician and referral as appropriate (b) (4)?
7. Are you planning to do additional animal studies that would examine the effect of the drug in males and their offspring?
8. Regarding the proposed (b) (4):

DRAFT

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/s/  
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MONA G PATEL  
10/19/2011

**eCTD NDA 203388/0  
vismodegib (Erivedge)  
Internal Team Meeting  
10-12-11**

Memorandum

**Date:** October 12, 2011

**From:** Mona Patel, DBOP/OODP/CDER

**Subject:** Internal Team Meeting: NDA 203388

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**Original Application:** NDA 203388

**Product:** vismodegib [Proper Name- Erivedge (under review)]  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

This internal meeting was held to discuss Genentech's proposed [REDACTED] (b) (4) It was concluded a telecon with sponsor was needed to discuss proposed [REDACTED] (b) (4)

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/s/  
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MONA G PATEL  
10/25/2011

**From:** [Mesmer, Deborah](#)  
**To:** ["Michelle Rohrer";](#)  
**cc:** [Gregory Gallegos; Joana Calvo; Winslow Nathan;](#)  
**Subject:** Vismodegib NDA 203388- CMC Information Request  
**Date:** Tuesday, October 11, 2011 2:46:08 PM

---

Dear Dr. Rohrer,

Please refer to NDA 203388 for vismodegib capsules. We have the following request for CMC information:

Provide dissolution profiles and actual individual test results (n=12, mean, minimum and maximum, RSD) for your pivotal Phase 2 and primary stability lots of drug product.

Please call me at the number below if you have any questions.

Sincerely,

Deborah Mesmer

**Deborah Mesmer**

Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)  
Division of New Drug Quality Assessment (DNDQA1)  
Food and Drug Administration  
White Oak Building 21, Rm 1627  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

(301) 796-4023

[deborah.mesmer@fda.hhs.gov](mailto:deborah.mesmer@fda.hhs.gov)

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DEBORAH M MESMER  
10/11/2011

SARAH P MIKSINSKI  
10/12/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): **OTS/OB/DBVI- Yi Tsong**

FROM (Name, Office/Division, and Phone Number of Requestor): **Debbie Mesmer, ONDQA- Project Manager for Quality**

DATE  
10/11/11

IND NO.

NDA NO.  
203388

TYPE OF DOCUMENT  
Original NDA

DATE OF DOCUMENT  
September 8, 2011

NAME OF DRUG  
vismodegib capsules, 150 mg

PRIORITY CONSIDERATION  
priority, expedited

CLASSIFICATION OF DRUG  
Type 1, DOP2

DESIRED COMPLETION DATE  
November 12, 2011

NAME OF FIRM: **Genentech, 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

- |   |   |
|---|---|
| <input 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

- |  |  |
|--|--|
| <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

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

**COMMENTS / SPECIAL INSTRUCTIONS:** Statistics consult review requested for the analysis of stability data in support of the proposed drug product shelf life

Indication: advanced basal cell carcinoma

OND Division: DOP2

Chemistry reviewer: Zedong Dong

CMC Lead: Liang Zhou

Please inform Debbie Mesmer of the assigned statistics reviewer.

Midcycle meeting: November 18, 2011

SIGNATURE OF REQUESTOR Deborah Mesmer	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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DEBORAH M MESMER  
10/11/2011

**From:** Patel, Mona

**Sent:** Tuesday, October 11, 2011 4:57 PM

**To:** 'Nathan Winslow'

**Cc:** Wen Liu

**Subject:** Response: FDA Information Requests: NDA 203388 (vismodegib)

1. For Question 7, FDA requests the raw data for *in vitro* studies, specifically for the CYP induction and inhibition studies. If this information has already been submitted, please provide the location in the eCTD.
2. For question 15, FDA requests the analysis datasets that support the NCA analysis. Either XPT or PWO format is acceptable as long as the individual data are listed and ready for performing analysis. Please also provide the dataset grouping by studies and patient type.

---

**From:** Nathan Winslow [mailto:winslow.nathan@gene.com]

**Sent:** Friday, October 07, 2011 1:44 AM

**To:** Patel, Mona

**Cc:** Wen Liu

**Subject:** Fwd: FDA Information Requests: NDA 203388 (vismodegib)

Dear Mona -

This email is to confirm Genentech (Roche) can respond to all the below questions related to the clinical pharmacology, nonclinical and microbiology sections by October 17th, except for Questions 7 and 15. For these two questions, we would like to request clarification to determine if responses to these can be provided in the requested timeframe, or as soon as possible otherwise.

For Question 7, could the Agency please clarify if raw data sets and SAS transport files for all "in vitro studies" are being requested? We believe this may be a typographical error and should read for all "in vivo studies." If the request for raw data sets is for all in vivo studies, please clarify if this is nonclinical or clinical PK data.

For clinical studies, SDTM domains PC and PP as well as other SDTM domains (EX, AE, DM, LB, VS) were submitted for each Clinical Study Report as well as CDISC ADaM domains for the Pharmacokinetic concentration and parameters.

For Question 15, please clarify if analysis datasets that support the NCA are requested (i.e., WinNonLin workspace files (.wsp) or WinNonLin data files (.pwo)) or source datasets to develop an analysis file for a NCA analysis are requested (i.e., SDTM PC, SDTM PP and other ADaM PK datasets).

For the request, please clarify what file format is required (XPT or PWO) and data grouping (by studies or by patient type).

Many thanks for clarifying these two specific requests,

Nathan

Begin forwarded message:

**From:** "Patel, Mona" <[Mona.Patel@fda.hhs.gov](mailto:Mona.Patel@fda.hhs.gov)>  
**Date:** October 5, 2011 6:42:04 PM GMT+02:00  
**To:** Wen Liu <[liu.wen@gene.com](mailto:liu.wen@gene.com)>  
**Subject:** FDA Information Requests: NDA 203388 (vismodegib)

Wen,

The following clinical pharmacology, nonclinical, and microbiology deficiencies were identified. We are requesting you provide a response back on these items no later than Monday, October 17, 2011. If this information has already been submitted, please provide the location in the eCTD. If you need additional time on some items, please let me know, and I will check with our team if it would be acceptable. Included in these requests are further IR's that were generated from Genentech's response sent to us via email on October 2, 2011 to our initial request sent to you on September 27, 2011 regarding proposed PMR language.

Please ack. receipt of this email and timeline for response.

1. Module 5.3.3 "*Reports of Human Pharmacokinetic Studies*" listed only three studies- SHH4433g, SHH4683g and SHH4610g. All clinical pharmacology study reports and raw data sets in electronic format (i.e., SAS transport files) should be included in Module 5.3.3. Please provide links to the studies that are not included in Module 5.3.3.
2. Please provide the analysis and table(s) listing the [I]/K<sub>i</sub> ratios for all the *in vitro* studies for CYP isoenzymes.
3. Please provide the relevant data (e.g. calculate [I]/IC<sub>50</sub> (or K<sub>i</sub>) ratio or net flux ratio) to determine whether vismodegib is a substrate or inhibitor of P-gp and BCRP. Refer to the following two links:  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269215.pdf>  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269213.pdf>
4. Please provide the relevant data to determine whether vismodegib is a substrate or inhibitor of OATP1B1 and OATP1B3. Refer to the following three links.  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269211.pdf>

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269216.pdf>

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269218.pdf>

5. Please provide a table listing different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies, if this is the case.
6. Please confirm that the formulation used in the food effect study SHH8395g is the to-be-marketed formulation.
7. Please provide the raw data sets and file definitions in electronic format (i.e., SAS transport files) for each of the in vitro studies. If this information has already been submitted, please provide the location in the eCTD.
8. Please provide interim report for DDI study SHH4593g, if it is available.
9. Please provide timelines for submitting the final study reports for food effect study SHH8395g and DDI study SHH4593g.
10. Please provide mile stone timelines for the renal and hepatic impairment trial (GP27839) as this trial will be conducted under post market requirement (PMR).
11. Please provide available dosing information with or without food in the phase 2 trials to assess the possible effect of food on exposure. It would be informative, if investigators or patients reported administration was mostly in a fasted state, or was mostly in a fed state.

(b) (4)

13. Please explain why you chose to report the single-dose PK (e.g. single-dose terminal  $t_{1/2}$  of 12 days) from the trials in healthy subjects, but not from the trials in BCC patients.

14. Please explain why you chose to report the multiple-dose PK (e.g. steady-state  $t_{1/2}$  of 4 days) from the PopPK analysis, but not from the NCA analyses for the trials in BCC patients.

15. Please provide the dataset that were used in the NCA analyses to obtain the PK parameters in healthy subjects and in BCC patients.

Nonclinical

16. Please provide dates as specified below.

Conduct a rodent carcinogenicity assessment according to the guidances for industry ICH S1B Testing for Carcinogenicity of Pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074916.pdf>) and ICH S1C (R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074919.pdf>) for further safety evaluation of vismodegib. The final protocols for the carcinogenicity studies will be submitted by XXXX, 201X, the studies will be completed by YYYY, 201Y, and the final study reports submitted by ZZZZ, 201Z.

#### Microbiology

17. It is understood that the microbial limits tests will be performed according to USP<61> and <62>. Provide the test methods for microbial limits testing along with data sets verifying the suitability of use of the stated microbial limits tests with the subject drug product.

As a FYI, please keep following IR's sent to your team for this application in mind when preparing future submissions that our division will be reviewing as to what our expectations are with regards to robustness of applications submitted to us. Multiple IR's hinder the review timeframe . Additionally, please keep in mind that proposed PMR's submitted should be presented to us in a manner one may find in an action letter which will always include dates for Final Protocol Submission, Trial/study completion, and Final Report Submission. With regards to the Final Report Submission date, it should be understood that the protocol should be final in regards to meeting the goals of the PMR at that milestone due date and therefore we recommend that Genentech submit the "final" protocol 60 days in advance of that date so FDA can review the protocol and identify any deficiencies that need to be addressed before the final protocol due date established.

Thank you,

Mona

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Biologic  
Oncology Products, Office of Oncology Drug Products, CDER, FDA | White Oak Complex, Bldg.  
22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993  
 [301.796.4236](tel:301.796.4236) (phone) • [301.796.9849](tel:301.796.9849) (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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MONA G PATEL  
10/11/2011

**From:** Jones, Karen  
**Sent:** Friday, October 07, 2011 5:35 PM  
**To:** 'wayson.sarah@gene.com'  
**Cc:** Patel, Mona  
**Subject:** NDA 203388 Information Request

Hello Dr. Wayson,

I am sending this information request to you on behalf of Mona Patel, the RPM assigned to your NDA. Please (b) (4) address them during your Applicant Orientation presentation scheduled to take place October 11, 2011.



Please confirm receipt of this email.  
Thank you.

Karen D. Jones  
Chief, Project Management Staff  
Division of Oncology Products 2  
Office of Hematology and Oncology Products

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MONA G PATEL  
10/11/2011

**From:** Patel, Mona  
**Sent:** Wednesday, October 05, 2011 12:42 PM  
**To:** 'Wen Liu'  
**Subject:** FDA Information Requests: NDA 203388 (vismodegib)

Wen,

The following clinical pharmacology, nonclinical, and microbiology deficiencies were identified. We are requesting you provide a response back on these items no later than Monday, October 17, 2011. If this information has already been submitted, please provide the location in the eCTD. If you need additional time on some items, please let me know, and I will check with our team if it would be acceptable. Included in these requests are further IR's that were generated from Genentech's response sent to us via email on October 2, 2011 to our initial request sent to you on September 27, 2011 regarding proposed PMR language.

Please ack. receipt of this email and timeline for response.

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3. Please provide the relevant data (e.g. calculate [I]/IC<sub>50</sub> (or K<sub>i</sub>) ratio or net flux ratio) to determine whether vismodegib is a substrate or inhibitor of P-gp and BCRP. Refer to the following two links:

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<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM269213.pdf>

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clinical studies or affirm that the to-be-marketed image was used in all studies, if this is the case.

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(b) (4)

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Nonclinical

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(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074919.pdf>) for further safety evaluation of vismodegib. The final protocols for the carcinogenicity studies will be submitted by XXXX, 201X, the studies will be completed by YYYY, 201Y, and the final study reports submitted by ZZZZ, 201Z.

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As a FYI, please keep following IR's sent to your team for this application in mind when preparing future submissions that our division will be reviewing as to what our expectations are with regards to robustness of applications submitted to us. Multiple IR's hinder the review timeframe . Additionally, please keep in mind that proposed PMR's submitted should be presented to us in a manner one may find in an action letter which will always include dates for Final Protocol Submission, Trial/study completion, and Final Report Submission. With regards to the Final Report Submission date, it should be understood that the protocol should be final in regards to meeting the goals of the PMR at that milestone due date and therefore we recommend that Genentech submit the “final” protocol 60 days in advance of that date so FDA can review the protocol and identify any deficiencies that need to be addressed before the final protocol due date established.

Thank you,

Mona

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Biologic Oncology Products, Office of Oncology Drug Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

📞 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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MONA G PATEL  
10/05/2011



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

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Teleconference Meeting Minutes

**Date:** September 29, 2011

**From:** Mona Patel, Pharm.D., DBOP/OODP/OND/CDER/FDA

**Subject:** NDA 203388: Clarify clinical site inspections

**Product:** Vismodegib for treatment of adult patients with advanced basal cell carcinoma  
[REDACTED] (b) (4)

**Meeting Date:** September 28, 2011, 1:00pm-1:30pm EST

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FDA Attendees:

Mona Patel – Regulatory Project Manager, Division of Oncology Products II  
Ke Liu, MD, Ph.D, Clinical Team Lead  
Lauren Iacono-Connors, Ph.D., Office of Scientific Investigations, CDER

Genentech, Inc. Attendees

Wen Liu, Ph.D., Global Regulatory Lead,  
Thirunellai Venkateshwaran, Ph.D., Director, Pharma Technical Regulatory  
Greg Gallegos, M.B.A., Regulatory Advisor, Pharma Technical Regulatory  
Bernd A Kraemer Ph.D., Head of Small Molecule Development Product Quality  
Minli Xie, Ph.D., Senior Scientist, Small Molecule Pharmaceutical Sciences  
Stacey Ma Ph.D., Head of Small Molecule Development Product Quality  
Glenn M. Corrington, Manager, Supplier Quality, Quality and Compliance  
Sueanne Lee, External Quality  
Barbara Lowe, Site Inspection Management, Quality  
Shashank Chatterjee, Technical Development Project Manager

FDA requested a teleconference with Genentech to review the clinical sites that the FDA intends to inspect, including the sponsor, contract research organizations (CROs) (independent review facility sites ((IRFS) and [REDACTED] (b) (4) that have generated or hold the data and records for pivotal study SHH4476g. For the following sites the FDA requested the information below. The FDA clarified that the purpose of the teleconference was to discuss clinical, and not manufacturing, issues.

### REQUEST 1:

In the vismodegib NDA application, there are three IRFs as CROs for primary endpoint assessment : (b) (4) for assessing radiography imagings and (b) (4) for photographic imaging, an independent pathologist reviewer from (b) (4) for biopsies and to determine efficacy-evaluable patients.

The FDA conveyed its intention to inspect all three IRF sites (b) (4) independent pathology review) and requested the following information:

1. Clarify the relationship of IRFs with Genentech:
  - o Transfer of Obligation Forms between Genentech and IRFs (Confirm and update Application as appropriate.)
  - o Contracts between Genentech and the IRFs,
2. Clarify the location of the IRF charters in the NDA
3. Provide the detailed addresses of IRFs, including point of contact (name and phone number)

*The FDA requested GENENTECH to provide this information as soon as possible, ideally by the end of the week (September 30<sup>th</sup>, 2011) to ensure inspection planning can be initiated rapidly.*

### REQUEST 2

FDA asked Genentech to clarify Genentech's responsibility as sponsor as opposed to CRO (b) (4) responsibilities and to clarify the location of pivotal study documents and records.

The FDA conveyed its intention to inspect the sponsor (Genentech) and review documents such as trial master files for the pivotal study, records that related to the specific responsibilities for the pivotal studies such as clinical investigator conduct and training, and oversight of the study, data management, adverse event reporting, and efficacy data collection, etc. If the records are held at the CRO, Genentech should inform the FDA.

*The FDA requested GENENTECH to provide this information as soon as possible, ideally by the end of the week (September 30<sup>th</sup>, 2011) to ensure inspection planning can be initiated rapidly.*

### REQUEST 3

FDA is planning clinical site inspections for those involved in the pivotal study. FDA requested Genentech to provide the data listings for all patients regarding the following information next week if possible:

All components of the overall response rate endpoint, serious adverse events, all deviations from protocols, and subject disposition. If there is a difference between how major and minor protocol deviations are defined, please clarify the criteria. FDA requested that the data be organized by clinical sites so that verification against source records would be possible by the Agency during inspection.

FDA indicated that this information should be provided next week (October 7, 2011).

All the information should be formally submitted to the NDA.

**CONCLUSION:**

Genentech confirmed that Wen Liu will be the Genentech point of contact for all clinical inspection coordination with the FDA.

The FDA indicated that the inspection related assignments for this application will be conducted quickly over the coming days to quickly facilitate clinical inspection planning, and have requested Genentech make every effort to provide responses as soon as possible.

Genentech agreed to provide response as rapidly as possible.

Call concluded.

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MONA G PATEL  
10/13/2011

**eCTD NDA 203388/0**  
**vismodegib (Erivedge)**  
**Second Planning (Team) Meeting Summary**  
**9-27-11**

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**Original Application:** NDA 203388

**Product:** vismodegib  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

**Current Review Team for NDA 203388:**

*Director:*  
Patricia Keegan

*Regulatory:*  
Mona Patel, Regulatory Project Manager  
Karen Jones (CPMS)

*Clinical:*  
Michael Axelson  
Ke Liu (TL and CDTL)

*Statistical:*  
Janet Xiaoping Jiang  
Kun He (TL)

*Clinical Pharmacology:*  
Jian Wang  
Hong Zhao (TL)

*Toxicology:*  
Dubravaka Kufrin  
Todd Palmby (TL)

*Product:*  
Anne Marie Russell  
Zedong Dong  
Liang Zhou (TL)

## Consults:

- |    |                             |   |
|----|-----------------------------|---|
| a. | DDMAC Reviewer              | Carole Broadnax - professional reviewer,<br>Karen Munoz - consumer reviewer<br>Olga Salis – RPM |
| b. | DSI Clinical Reviewer       | Lauren Iacono-Connor  |
| c. | OSE (DRISK) Reviewer (REMS) | Amarilys Vega   |
| d. | DMEPA (proprietary name)    | Rick Abate- Safety Evaluator  |
| e. | SEALD Reviewer              | No assignment   |
| f. | Maternal Health:            | Tammie B. Howard  |
| g. | Facility Reviewers:         | Mahesh Ramanadham   |
| h. | Microbiology Consult:       | John Metcalfe   |
| i. | BioPharma Consult:          | Zedong Dong   |
| j. | QT-IRT Consult              | Devi Kozeli   |
| k. | Pediatric Page/Perc Review; | Full waiver requested   |

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

## Agenda Items:

1. **Calendar**
2. **Timeline-Inspections**
  - a. DSI  
**Discussion:** *Telecon with Genentech required to clarify few inspection-related questions. RPM will schedule one asap.*
  - b. Facilities  
**Discussion:** *Facilities will try its best to complete manufacturing inspections within 5 month review timeline. Can not commit to a specific date at this time.*

(b) (4)

4. **Review Status:**

Priority Review: Office has requested taking action within 5 months (Division Action Date: February 3, 2012. Can we work towards this goal?)  
**Discussion:** *Yes, however CMC will not be able to provide primary review until January 20, 2012 at the earliest.*

5. **Updates:**

- a. Filing Meeting Date: October 4, 2011.  
**Discussion:** *Reviewers reminded to bring filing reviews to meeting and upload into DARRTS.*
- b. Applicant Orientation Presentation: October 11, 2011 12-1pm
- c. Technical Walk-Through: October 11, 2011 1-2pm
- d. PeRC Meeting Date: October 12, 2011. Meeting invites sent to clinical, nonclinical, and clinical pharmacology. Would anyone else like to be invited to attend? Due date for forwarding materials to PeRC for review is COB October 3, 2011 (please send to me by 3pm October 3, 2011).  
**Discussion:** *Clinical agreed to send materials to RPM to forward to PeRC by 3pm Monday, October 3, 2011.*
- e. Mid-Cycle Meeting Date: November 18, 2011 2-3pm EST. Would you like for me to schedule a mid-cycle planning meeting? If so, when?  
**Discussion:** *No mid-cycle planning meeting needed. Review team acknowledged Dr. Pazdur's request for each presenter to focus on major issues only and to do so in a concise manner not to exceed 10 minutes per presenter.*
- f. Labeling Meetings (see attached calendar)  
**Discussion:** Labeling meetings will be held on November 29 and 30, 2011 and December 2, 9, and 13, 2011.
- g. Categorical Exclusion: Will CMC address in primary review or be writing a separate review for this?  
**Discussion:** CMC will include in primary review.
- h. Where do we stand on SGE's? Besides a physician consultant is a patient consultant needed?  
**Discussion:** *No, patient consultant is not needed. Clinical will be contacting prospective SGE's to ascertain interest.*
- i. Need for carcinogenicity studies  
**Discussion:** *Genentech has noted they will be conducting postmarketing carcinogenicity studies. RPM to contact Genentech to submit specific PMR language for PMR's.*
- j. Confirm Review Deadline  
**Discussion:** *Review team, with exception of CMC, will target for January 6, 2012 to complete primary reviews.*

**Additional points to be discussed:**

*None*

**Action Items:**

- a. Set up team meetings to occur every 3 weeks
- b. Set up Wrap-Up Meeting
- c. Set up a meeting to discuss (b) (4)

The meeting concluded.

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/s/  
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MONA G PATEL  
10/13/2011

**From:** Patel, Mona  
**Sent:** Tuesday, September 27, 2011 10:42 PM  
**To:** 'Wen Liu'  
**Subject:** FDA Information Request: NDA 203388

Wen,

1. Please tell us if a pediatric plan has been drafted for the US and EMA. If one has been drafted, please email it to us and submit it formally to NDA 203388.

2. Also, please email me the proposed PMR's you plan to conduct under this application. Specifically, we are looking for the proposed language you want for each PMR.

Please provide a response to the first item by Noon Friday, 9.30.11. For the second one, please submit a response by Noon Monday, 10.3.11.

Please ack. receipt of email.

**Mona**

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Biologic Oncology Products, Office of Oncology Drug Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993

 301.796.4236 (phone) • 301.796.9849 (fax) | [mona.patel@fda.hhs.gov](mailto:mona.patel@fda.hhs.gov) (email)



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/s/  
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MONA G PATEL  
09/27/2011

**From:** Patel, Mona  
**Sent:** Monday, September 26, 2011 12:21 PM  
**To:** 'Wen Liu'  
**Subject:** FDA Request: Clinical Pharmacology Table NDA 203388

Wen,

Please fill out the attached clinical pharmacology form and email it back to me by 10am EST, Wednesday, 9.28.11.

Thanks,

Mona

**Table 1. Highlights of Clinical Pharmacology**

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with

		mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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/s/  
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MONA G PATEL  
09/27/2011



NDA 203388

**NDA ACKNOWLEDGMENT**

Genentech, Inc.  
Attention: Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Rohrer:

We have received your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: vismodegib, 150 mg capsules

Date of Application: September 8, 2011

Date of Receipt: September 8, 2011

Our Reference Number: NDA 203388

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 November 7, 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).

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 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

If you have any questions, call Dr. Mona Patel, Regulatory Project Manager, at (301) 796-4236.

Sincerely,

*{See appended electronic signature page}*

Karen D. Jones  
Chief, Project Management Staff  
Division of Drug Oncology Products 2  
Office of Hematology Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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KAREN D JONES  
09/22/2011

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**From:** Patel, Mona  
**Sent:** Wednesday, September 21, 2011 10:36 PM  
**To:** 'Wen Liu'  
**Subject:** Applicant Orientation General Advice: vismodgeib NDA 203388

Wen,

Attached is general advice we provide to all sponsor's for a applicant orientation presentation.

Please acknowledge receipt.

## **OODP's General Advice for Application Orientation Presentation Meetings**

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OODP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

### **Administrative:**

1. Sponsor attendees
2. Presentation outline or Agenda. Should list sections included in submission.

### **Background and Application Specifics:**

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.
4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.
5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.

6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.
7. Regulatory history, including the following:
  - Orphan Drug designation, Fast Track designation
  - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
  - Key Outcomes from FDA Interactions
    - EOP2 Meeting
    - Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
    - Pre-NDA/BLA meeting
    - Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

**Summary Content of NDA/BLA/Efficacy Supplement Sections:**

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

You should also present results of the following, as appropriate:

- Clinical study sites (foreign or domestic)
- Biomarker development for population selection (if applicable)
- Assay validation (if applicable)

120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data
10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
  - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.
11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities
12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics

(metabolic pathway, metabolites,  $t_{1/2}$ , ADME, PK in special populations, drug-drug interactions).

13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU)).
14. Risk/benefit profile for drug/biologic
15. Summary
16. Q & A

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/s/

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MONA G PATEL  
09/22/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): IRT/QT

FROM (Name, Office/Division, and Phone Number of Requestor): Mona Patel  
RPM/DOP2, 301-796-4236

DATE September 21, 2011,	IND NO.	NDA NO. 203388	TYPE OF DOCUMENT Original NDA/NME	DATE OF DOCUMENT 9/8/2011
NAME OF DRUG vismodegib (Erivedge)	PRIORITY CONSIDERATION Priority (Div targeting 2/3/2012)	CLASSIFICATION OF DRUG Oncology (small molecule)	DESIRED COMPLETION DATE (TBD)	

NAME OF FIRM: Genentech, 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 checked="" 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 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 type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

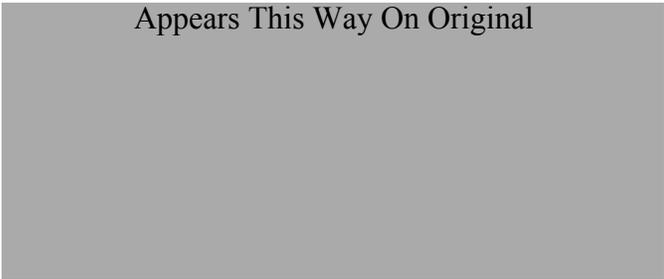
#### COMMENTS / SPECIAL INSTRUCTIONS:

Genentech submitted an original NDA (NME) for vismodegib (Erivedge) for treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b)(4). Genentech submitted 2 QTc studies in healthy subjects and BCC patients we would like a review for. The application can be accessed at \\CDSESUB5\EVSPROD\NDA203388\203388.enx. We are requesting reviewer presence/input throughout application review process. Upcoming meetings that have been scheduled already and would like the reviewer to be made aware of is 9/27/11 from 11-12pm (2<sup>nd</sup> Planning Mtg) and 10/4/11 from 2-3pm (Filing Meeting).

SIGNATURE OF REQUESTOR Mona Patel	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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MONA G PATEL  
09/21/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): CDER/SEALD  
Study Endpoints and Labeling  
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411  
SEALD.ENDPOINTS@FDA.HHS.GOV

FROM (Name, Office/Division, and Phone Number of Requestor): Mona Patel  
RPM/DOP2, 301-796-4236

DATE  
September 21, 2011,

IND NO.

NDA NO.  
203388

TYPE OF DOCUMENT  
Original NDA/NME

DATE OF DOCUMENT  
9/8/2011

NAME OF DRUG  
vismodegib (Erivedge)

PRIORITY CONSIDERATION  
Priority (Div targeting  
2/3/2012)

CLASSIFICATION OF DRUG  
Oncology (small  
molecule)

DESIRED COMPLETION DATE  
Before labeling meetings  
(TBD)

NAME OF FIRM: Genentech, Inc.

## REASON FOR REQUEST

### I. GENERAL

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| <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 checked="" 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 type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <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       |
| <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): |
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### 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"/> 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 type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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### COMMENTS / SPECIAL INSTRUCTIONS:

Genentech submitted an original NDA (NME) for vismodegib (Erivedge) for treatment of adult patients with advanced basal cell carcinoma (b)(4). Genentech submitted labeling we would like a SEALD review for. The application can be accessed at \\CDSESUB5\EVSPROD\NDA203388\203388.enx. We are requesting reviewer presence/input throughout application review process, but most specifically at labeling meetings. Upcoming meetings that have been scheduled already and would like the reviewer to be made aware of is 9/27/11 from 11-12pm (2<sup>nd</sup> Planning Mtg) and 10/4/11 (Filing Meeting).

SIGNATURE OF REQUESTOR  
Mona Patel

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/s/  
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MONA G PATEL  
09/21/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): **Maternal Health**

FROM (Name, Office/Division, and Phone Number of Requestor): **Mona Patel,  
301-796-4236**

DATE <b>September 21, 2011, 2011</b>	IND NO.	NDA NO. <b>203388</b>	TYPE OF DOCUMENT <b>Original</b>	DATE OF DOCUMENT <b>9/8/2011</b>
NAME OF DRUG <b>visomedogib (Erivedge)</b>	PRIORITY CONSIDERATION <b>Priority (Div targeting 2/3/2012</b>	CLASSIFICATION OF DRUG <b>NME</b>	DESIRED COMPLETION DATE <b>Before Mid-Cycle Meeting (TBD)</b>	

NAME OF FIRM: **Genentech**

## REASON FOR REQUEST

### I. GENERAL

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| <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 checked="" 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 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

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

#### COMMENTS / SPECIAL INSTRUCTIONS:

Genentech submitted a original NDA (NME) for vismodegib (Erivedge) for treatment of adult patients with advanced basal cell carcinoma (b)(4). Genentech submitted a Med Guide and PI. The application can be accessed at \\CDSESUB5\EVSPROD\NDA203388\203388.enx. We are requesting reviewer presence/input throughout application review process. Upcoming meetings that have been scheduled already and would like the reviewer to be made aware of is 9/27/11 from 11-12pm (2<sup>nd</sup> Planning Mtg) and 10/4/11 (Filing Meeting).

SIGNATURE OF REQUESTOR <b>Mona Patel</b>	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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/s/  
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MONA G PATEL  
09/21/2011

**eCTD NDA 203388/0**  
**vismodegib (Erivedge)**  
**Planning Meeting Summary**  
**9-20-11**

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**Original Application:** NDA 203388

**Product:** vismodegib  
**Submission Date:** September 8, 2011  
**Received Date:** September 8, 2011  
**Sponsor:** Genentech, Incorporated  
**Indication:** For the treatment of adult patients with advanced basal cell carcinoma [REDACTED] (b) (4)

**Current Review Team for NDA 203388:**

*Director:*  
Patricia Keegan

*Regulatory:*  
Mona Patel, Regulatory Project Manager  
Karen Jones (CPMS)

*Clinical:*  
Michael Axelson  
Ke Liu (TL and CDTL)

*Statistical:*  
Janet Xiaoping Jiang  
Kun He (TL)

*Clinical Pharmacology:*  
Jian Wang  
Hong Zhao (TL)

*Toxicology:*  
Dubravaka Kufrin  
Todd Palmby (TL)

*Product:*  
Anne Marie Russell  
Zedong Dong

Liang Zhou (TL)

**Consults:**

- |    |                             |   |
|----|-----------------------------|---|
| a. | DDMAC Reviewer              | Carole Broadnax - professional reviewer,<br>Karen Munoz - consumer reviewer<br>Olga Salis – RPM |
| b. | DSI Reviewer                | Draft consult sent to clinical on 9.14.11   |
| c. | OSE (DRISK) Reviewer (REMS) | Amarilys Vega   |
| d. | DMEPA (proprietary name)    | Rick Abate- Safety Evaluator  |
| e. | SEALD Reviewer              | To be requested   |
| f. | Maternal Health:            | Is one needed? <i>Yes</i>   |
| g. | Facility Reviewers:         | TBD   |
| h. | Microbiology Consult:       | John Metcalfe   |
| i. | BioPharma Consult:          | Zedong Dong   |
| j. | QT-IRT Consult              | To be requested   |
| k. | Pediatric Page/Perc Review; | Full waiver requested:  |

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

**Agenda Items:**

1. **Review Status:**

- a. Priority Review requested  
**Discussion:** *Office would like to take action in 4 months due to the application being intended for an unmet medical need. Review team did not think this was feasible. A 5 month review timeframe was suggested instead. Review team will consider their competing priorities and re-visit this at a second planning meeting to occur within 1 week. Ke Liu accepted role of CDTL for this application.*
- b. Categorical Exclusion requested
- c. Request for waiver of pediatric studies  
**Discussion:** *RPM will schedule a time for review team to meet with PeRC in early December.*
- d. Since October 2006, the clinical development of vismodegib has been conducted under IND 74,573. Applicant cross-references IND 103846 for NCI Protocol 8395.

2. **Dates Milestone Letters Must Issue (assuming a priority 6 month clock):**

- a. Acknowledgment letter- Dated 9/22/11

- b. Filing Action Letter: 11/7/11: Do we have any filing issues that we should discuss? If the filing issues are not identified by then, should we send a “Notification of Review Status”?  
**Discussion:** *This topic will be re-visited at the filing meeting.*
- c. Deficiencies Identified Letter (74 day letter): 11/21/2011
- d. Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s target date (based on 4 month action) is 12/ 9/2011), what is our Target Date?  
**Discussion:** *This topic will be re-visited at second planning meeting after RPM has re-run the review planner to take into consideration a 5 month review timeline.*
- e. Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant (Review Planner’s target date (based on 4 month action) is 12/16/2011), what is our Target Date?  
**Discussion:** *This topic will be re-visited at second planning meeting. RPM will re-run the review planner to take into consideration a 5 month review timeline.*

(b) (4)

- f. Action Letter: Division Goal: January 6, 2012  
**Discussion:** *RPM will re-run the review planner to take into consideration a 5 month review timeline.*

3. **Upcoming Internal Team Meetings:**

- a. **Filing Meeting:** To be scheduled  
**Discussion:** *RPM will have date scheduled by time of second planning meeting. Review team requested to bring Filing review (TL signature) and Interim Deliverables and to be prepared to identify significant filing issues for day 74 letter.*
- b. **Mid-Cycle Meeting:** TBD  
**Discussion:** *RPM will have date scheduled by time of second planning meeting.*
- c. **Labeling Meetings:** To be scheduled  
**Discussion:** *RPM will have date scheduled by time of second planning meeting.*

- d. **Team Meetings and PMR/PMC Working meetings:** Would you like to have team meetings? If so, how frequently?  
**Discussion:** *Yes, every 3 weeks*
  - e. **Wrap- Up Meeting:** TBD (Will set-up right after last labeling meeting)  
**Discussion:** *RPM will have date scheduled by time of second planning meeting.*
4. **Applicant Orientation Presentation: (45 Day Clock 10/23/2011)**
- No availability during Monday Oncology Meeting. RPM will try to schedule AOP to be held within 3 weeks.
- The advice document regarding AOP will be sent to the sponsor. Is there anything specific that you would like for me to communicate with Sponsor prior to this meeting?
- Discussion:** *RPM asked to try and schedule for week of October 10, 2011.*
5. **ODAC Needed:**
- Discussion:** *No. The application did not raise significant safety or efficacy issues.*
6. **Miscellaneous Items or Issues:**
- a. Please bring Filing Review Memos to the Filing Meeting. The template is available on the 21<sup>st</sup> Century website.
  - b. Do we need preclinical study site Audits?  
**Discussion:** *No*
  - c. Advisory Committee- Planning the meetings (Planning meeting and Practice meetings)  
**Discussion:** *No, as ODAC will not be held.*
  - d. Propriety name review request: Submitted to IND 74573 on August 2, 2011. Included in original NDA submission (90 Day Clock 12/7/11)  
**Discussion:** *OSE RPM will request document room to double code supporting document 1 under NDA 203388 as a proprietary name review request. OSE committed to complete review by 90 Day Goal Date of 12/7/2011.*
  - e. Will or has Clinical pharmacology identified any early PMC/PMRs?  
**Discussion:** *Too early to say, but most likely 2-3 PMR's will be required for this application.*
  - f. When to invite DDMAC and OSE during the labeling meeting?

**Discussion:** *RPM to invite DDMAC at labeling meetings when label is substantially complete. Once agenda for labeling meetings is established, OSE will accept labeling meetings as appropriate.*

- g. Do we need to have a teleconference with the Applicant before the filing meeting?  
**Discussion:** *No*
- h. Tu-Van Lambert will process the following consults:
  - **Establishment (EES)**
  - **Compliance**
  - **Environmental Assessment****Discussion:** *CMC acknowledged.*
- i. Pre-approval facility inspections and discussion with ONDQA and DMPQ  
**Discussion:** *CMC RPM will follow-up with request for facility assignment as will clinical RPM.*
- j. Review Target due dates:  
Primary Review due: December 9, 2011 (4 weeks before Action)  
Secondary Review due: December 13, 2011 (3 1/2 weeks before action)  
**Discussion:** *Review deadlines will be re-visited at second planning meeting in accordance with a 5 month review timeline.*
- k. Compile and circulate Action Letter and Action Package- Target date- December 16, 2011.  
Start to draft Approval Letter by:  
Send the draft of Approval letter to Jeff Summers by:  
**Discussion:** *Send draft of Approval letter to Dr. Jeff Summers at least 3 weeks before action date. RPM to draft Action letter in accordance with this timeline.*
- l. Action Date March 6, 2012  
**Discussion:** *RPM requested to calculate a 5 month action date*

**Additional points discussed:**

*Dr. Richard Pazdur will be signatory authority on application.*

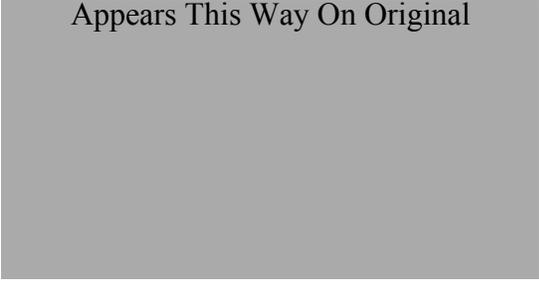
**Action Items:**

*Discuss need for carcinogenicity studies at second planning meeting*

*Request consults for Maternal Health, SEALD, IT-QRT,*

*The meeting concluded.*

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/s/  
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MONA G PATEL  
10/13/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): Environmental Assessment Group/SRS  
Attn: Raanan Bloom and/or Emily McVey

FROM (Name, Office/Division, and Phone Number of Requestor): Tu-Van Lambert, Regulatory Project Manager, Office of New Drug Quality Assessment

DATE September 20, 2011	IND NO.	NDA NO. 203388	TYPE OF DOCUMENT 505(b)(1) new NDA, NME	DATE OF DOCUMENT September 8, 2011
NAME OF DRUG vismodegib capsules		PRIORITY CONSIDERATION priority review	CLASSIFICATION OF DRUG oncology drug	DESIRED COMPLETION DATE November 1, 2011 or as soon as feasible

NAME OF FIRM: Genentech 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 checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT                    | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                     |
| <input checked="" 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

- |   |   |
|---|---|
| <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

- |  |  |
|--|--|
| <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

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

COMMENTS / SPECIAL INSTRUCTIONS: This new NDA is a 505(b)(1) for the treatment of adult patients with advanced basal cell carcinoma (b)(4). Please review the NDA's environmental assessment. Submissions can be found in DARRTS: \\Cdsub1\evsprod\nda203388  
DOP2 is requesting accelerated review so expediting review appreciated

OND/OHOP/DOP2 RPM: Mona Patel  
PDUFA date: March 8, 2012; Action Date: TBD

SIGNATURE OF REQUESTOR Tu-Van Lambert	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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TU-VAN L LAMBERT  
09/20/2011

# REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) Mona Patel RPM/DOP2; 301-796-4236 DOP2/OHOP/OODP/OND/CDER/FDA
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REQUEST DATE September 15, 2011	IND NO.	NDA/BLA NO. 20388/0	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) NME/ Original NDA, Submitted and Received 9/8/11
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NAME OF DRUG vismodegib (ERIVEDGE)	PRIORITY CONSIDERATION Priority Review (6 months)	CLASSIFICATION OF DRUG Oncology (Small Molecule)	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) TBD
---------------------------------------	--	---	---

NAME OF FIRM: Genentech, Inc.	PDUFA Date: March 8, 2012
----------------------------------	---------------------------

## TYPE OF LABEL TO REVIEW

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" 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)	<b>TYPE OF APPLICATION/SUBMISSION</b> <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	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
--	--	--

**EDR link to submission:** <\\CDSESUB5\EVSPROD\NDA203388\203388.enx>

**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. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: TBD

Labeling Meetings: TBD

Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER  
Mona Patel

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

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/s/  
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MONA G PATEL  
09/16/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): OSE/DRISK

FROM (Name, Office/Division, and Phone Number of Requestor): Mona Patel  
RPM/DOP2; 301-796-4236  
DOP2/OHOP/OND/CDER/FDA

DATE September 15, 2011	IND NO.	NDA NO. 203388/0	TYPE OF DOCUMENT NME/ Original NDA	DATE OF DOCUMENT 9/8/11
NAME OF DRUG vismodegib (GDC-0449)		PRIORITY CONSIDERATION Priority Review (6 months)	CLASSIFICATION OF DRUG Oncology (Small Molecule)	DESIRED COMPLETION DATE TBD

NAME OF FIRM: Genentech, 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 checked="" 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 type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input 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

- |  |  |
|--|--|
| <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

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

COMMENTS / SPECIAL INSTRUCTIONS: DOP2 is requesting OSE (DRISK) to review the label and proposed (b) (4) submitted in the original NDA 203388/0. Labeling meeting invitations will be sent to the assigned OSE reviewer. The Sponsor's proposed labeling can be found in the EDR under STN 203388/0 as an eCTD submission. The action goal date for this original application is 03/8/12; consult review of this application is TBD.

SIGNATURE OF REQUESTOR Mona Patel, RPM	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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MONA G PATEL  
09/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO (Division/Office): **New Drug Microbiology Staff**

**E-mail to: CDER OPS IO MICRO**

**Paper mail to: WO Bldg 51, Room 4193**

FROM: Tu-Van Lambert, Product Quality RPM, Office of New Drug Quality Assessment, WO 21 Room 2625, (301) 796-4246  
PROJECT MANAGER (if other than sender):

REQUEST DATE  
September 14, 2011

IND NO.

NDA NO.  
203388

TYPE OF DOCUMENT  
New NDA, (b)(1), NME

DATE OF DOCUMENT  
September 8, 2011

NAMES OF DRUG  
Vismodegib (GDC-0449)

PRIORITY CONSIDERATION  
TBD

PDUFA DATE  
March 8, 2012 (if Priority)  
July 8, 2012 (if Standard)

DESIRED COMPLETION DATE  
January 8, 2012 (if Priority)  
May 8, 2012 (if Standard) or  
TBD

NAME OF APPLICANT OR SPONSOR: Genentech

### GENERAL PROVISIONS IN APPLICATION

- |  |   |
|--|---|
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED                                     | <input type="checkbox"/> CBE-0 SUPPLEMENT                     |
| <input checked="" type="checkbox"/> NDA FILING REVIEW NEEDED BY: <u>November 7, 2011</u> | <input type="checkbox"/> CBE-30 SUPPLEMENT                    |
| <input type="checkbox"/> BUNDLED   | <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY |
| <input checked="" type="checkbox"/> DOCUMENT IN EDR                                      |   |

### COMMENTS / SPECIAL INSTRUCTIONS:

This new NDA is for vismodegib for the treatment of adult patients with advanced basal cell carcinoma (b)(4) (b)(4) Application references IND 074573 and pre-NDA meetings dated May 10, 2011 (CMC) and May 11, 2011 and Type C meeting April 29, 2011. Micro review requested to review microbial limits in drug product and any microbiology content provided in this new NME NDA.

Link to EDR: <\\Cdsub1\evsprod\nda203388>

Please contact the OND RPM Mona Patel for updates to review timelines and review completion dates.

SIGNATURE OF REQUESTER Tu-Van Lambert

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS  EDR  E-MAIL  MAIL  HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR  E-MAIL  MAIL  HAND

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TU-VAN L LAMBERT  
09/14/2011



FOOD AND DRUG ADMINISTRATION

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**Meeting Date and Time:** May 11, 2011 3 PM- 4 PM  
**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA  
**Meeting Location:** WO 22, Room 1313  
**Application Number:** IND 074573  
**Product Name:** GDC-0449 (Hedgehog Pathway Inhibitor)  
**Received Briefing Package** April 11, 2011  
**Sponsor Name:** Genentech Inc.  
**Meeting Requestor:** Matthew Klimek, Pharm D.  
**Meeting Chair:** Ke Liu, MD, PhD  
**Meeting Recorder:** Yolanda G. Adkins, R.N., MSHA

**Meeting Attendees:**

**FDA Attendees:**

Richard Pazdur, M.D., Director, OODP  
Anthony Murgo, M.D., Associate Director, OODP  
Ke Liu, M.D., Ph.D., Clinical Team Leader, DDOP  
Amna Ibrahim M.D., Division Deputy Director, Clinical Team Leader, DDOP, OODP  
Michael Brave, M.D., Medical Officer, DDOP  
Katherine Fedenko, M.S., CRNP, Senior Clinical Analyst, DDOP  
Haleh Saber, Ph.D., PharmTox Acting Team Leader, DHP  
Wei Chen, Ph.D. PharmTox Reviewer, DHP  
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCP5  
Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer, DCP5  
Shenghui Tang, Ph.D., Biostatistics Team Leader, DBV  
Lijun Zhang, Ph.D, Biostatistics Reviewer, DBV  
Suzanne Robottom, Team Leader, DRISK  
Jamila Mwidau, Regulatory Project Manager, DDOP  
Sarah Simon, Regulatory Project Manager, OSE

**External Attendees:**

Noël Dybdal, D.V.M., Ph.D., DACVP Associate Director, Safety Assessment - Pathology

Richard Graham, Ph.D. Pharmacology Subteam Lead, Clinical Pharmacology

Israel Gutierrez, M.D. Senior Global Safety Science Lead, Oncology, Global Risk Management

Gladys Ingle, Senior Associate, Product Development Regulatory

Karen Jones, Global Head Oncology, Product Development Regulatory

Chin-Yu Lin, Ph.D. Associate Director, Product Development Biostatistics

Wen Liu, Ph.D. Vismodegib Global Regulatory Lead, Product Development Regulatory

Jennifer Low, M.D., Ph.D. Assoc. Group Medical Director, Global Development Team Leader,  
Product Development Oncology

Howard Mackey, Ph.D. Senior Statistical Scientist, Product Development

Eric Morinello, Ph.D., DABT Toxicology Scientist, Safety Assessment - Toxicology

Josina Reddy, M.D., Ph.D. Senior Medical Director, Product Development Oncology

Iris Roth, Ph.D. Life Cycle Leader, Global Product Strategy

Sarah Wayson, Ph.D. Regulatory Scientist, Product Development Regulatory

Nathan Winslow, Associate Director, Product Development Regulatory

**1.0 BACKGROUND**

The sponsor is studying GDC-0449 (Hedgehog Pathway Inhibitor) IND 074573 for the treatment of patients with advanced basal cell carcinoma (BCC) (b)(4). The sponsor submitted a Type B Pre-NDA meeting request on January 31, 2011. The background package was received on April 11, 2011. To facilitate the meeting, the FDA sent the sponsor preliminary responses on May 5, 2011.

Vismodegib is a small molecule, orally administered inhibitor of the hedgehog pathway. Genentech is proposing to submit an NDA for vismodegib for the proposed indication of treatment of patients with advanced basal cell carcinoma (BCC) (b)(4). (b)(4)

The proposed efficacy database for this NDA would contain 137 patients. These 137 patients would include 104 patients (33 with metastatic BCC and 71 with locally advanced BCC) from a single-arm phase 2 trial (SHH4476g) plus a subset of 33 patients who had locally advanced or metastatic BCC in a phase 1 trial (SHH3925g). Genentech's analysis of SHH4476 found 10 of 33 (30%) patients with metastatic BCC and 27 of 71 (38%) patients with locally advanced BCC

to have achieved a partial response to vismodegib; no complete responses were reported. The median duration of all partial responses was 7.6 months.

The proposed safety database would contain 138 patients, including the 137 patients in the efficacy database plus one additional patient who had BCC from a pharmacokinetic study (SHH4610g). Common adverse events ( $\geq 20\%$ ) in SHH4476g were muscle spasms, alopecia, dysgeusia, weight decreased, fatigue, nausea, decreased appetite, and diarrhea. Genentech proposes to submit additional primary data from a randomized, placebo controlled clinical trial (SHH4489g) in patients with ovarian cancer but not include that data in the safety database.

The sponsor requested this Pre-NDA meeting to discuss the proposed BLA submission.

## 2.0 DISCUSSION

### Clinical Data:

1. Does the Agency agree that the data from the pivotal single-arm study SHH4476g along with supportive efficacy and safety data as outlined in this briefing package are adequate and sufficiently complete to form the basis of an NDA seeking full approval of the proposed indication?

Vismodegib as treatment for patients with advanced basal cell carcinoma (b) (4)

### FDA Response:

**This is a review issue.**

### Sponsor Clarification Request:

Genentech acknowledges that determination of the ability of data from SHH4476g and other supportive studies to support the registration of vismodegib for the proposed indication is a review issue. However, we would like to understand whether the proposal, as specified in the pre-meeting package, is sufficient to enable review of the NDA?

### Discussion:

**The Sponsor inquired whether the information contained in briefing package is sufficient to support the filing of the proposed NDA. FDA stated that the available information does not appear to indicate significant issues for filing. However, this will be a review issue at the time of submission.**

2. Does the Agency agree with Genentech's proposal for using the protocol-defined primary and secondary efficacy analyses for Study SHH4476g as the basis for the "Clinical Study" section of the package insert (see [Section 3.1](#))?

**FDA Response:**

**This is a review issue.**

**Please clarify the following inconsistency on the primary efficacy analysis population: "All efficacy analyses will be performed using all-treated patient population" specified in the SAP and "The primary analysis population included patients who had confirmed BCC at baseline" specified in the protocol synopsis and the efficacy data summary (Section 3.1).**

Sponsor Clarification Request:

Genentech has noted that a previous version of the SAP (original SAP, dated 28 July 2008) was erroneously appended to our pre-meeting package. The correct and final version of the SAP (Amendment 1, dated 17 November 2008) has been attached to this response document as Appendix A.

Briefly, regarding the primary efficacy analysis population, based on Agency feedback during SPA discussions, Genentech amended the SAP to include only patients with confirmed BCC at baseline in the primary efficacy analysis:

Section 3.3 of the SAP:

*"Unless otherwise noted, all efficacy analyses will be performed using the all-treated patient population, defined as all enrolled patients who receive any amount of study drug. Patients for whom the independent pathologist's interpretation of archival tissue or baseline biopsy is not consistent with BCC will not be included in the efficacy analyses. In locally advanced BCC cases where there is a conflicting interpretation of archival tissue versus a baseline biopsy by the independent pathologist, the baseline biopsy will be used to determine inclusion in the efficacy analyses."*

Does the Agency have any further comments or questions regarding the primary efficacy analysis population?

**Discussion:**

**The Agency will look at the efficacy analyses using the all-treated population as well as the efficacy-evaluable population.**

3. The Sponsor has provided several sensitivity analyses to address the comments received from the Agency during the SPA discussions and to assist with the interpretation of the efficacy results (see [Section 3.1.2.c](#) for details). Does the Agency agree that these sensitivity analyses are sufficient?

**FDA Response:**

**This is a review issue. We consider sensitivity analyses to be exploratory.**

**Sponsor Clarification Request:**

Genentech appreciates the Agency's comments and agrees that the sensitivity analyses included in the briefing package are exploratory. These are intended to address Agency comments made during SPA discussions and provide supporting rationale for the primary analysis as defined in the protocol and statistical analysis plan.

Based on the information included in the PMP, we would like to understand if there are any additional analyses that the Agency would like included in the NDA to help facilitate review?

**Discussion:**

**Additional sensitivity analyses if required will be requested during the review period.**

4. Does the Agency agree with the proposed analysis plan for the Integrated Summary of Safety for the advanced BCC patient population (see [Section 7.4](#))?

**FDA Response:**

**Your safety database as currently proposed would contain 138 patients. This would be a limited safety database to support approval of a new molecular entity. We note that you plan to submit datasets for Trial SHH4489g, but you do not intend to include those patients in the safety database. Please clarify why the safety data from the study will not be included in the safety database.**

**Sponsor Clarification Request:****SHH4489g**

Genentech appreciates the Agency's feedback to ensure an appropriate safety database to support approval of vismodegib. To clarify, we proposed that the NDA submission include the datasets with the CSR from Study SHH4489g in ovarian cancer patients because it is a randomized placebo-controlled single-agent vismodegib study (Module 5). Safety analyses

and discussion of the results of this study will also be included as part of the Summary of Clinical Safety (Module 2).

Could the Agency please clarify if the suggestion is to include a separate summary of the SHH4489g safety data as proposed or to integrate these data into the pooled safety analysis?

#### Safety Database Size

To clarify, the SCS (Module 2) of the NDA will include discussion of all patients exposed to vismodegib to date (> 450 on studies under Genentech IND 74,573 and > 300 on NCI-CTEP studies and ISTs ) including the following:

- Pooled safety analysis of data from advanced BCC patients enrolled on studies SHH4476g, SHH3925g, SHH4437g, and SHH4610g (n=138). We have proposed that the corresponding integrated safety datasets be provided in Section 5.3.5.3 and not to include data from studies of other indications.
- Safety analyses of the randomized Phase II studies SHH4489g and SHH4429g.
- Safety analyses of the Phase I studies SHH3925g and SHH4318g.
- Safety analyses of the clinical pharmacology studies SHH4610g, SHH4683g and SHH4433g.
- Safety analyses of the QTc Study SHH4871g.
- Summary safety information from the US Expanded Access study SHH4811g, from NCI CTEP-sponsored studies conducted under IND 103,846 and from other Investigator-Sponsored studies.

The ISS will present pooled summaries of demographics and baseline characteristics, drug exposure, adverse events, and laboratory toxicities from aBCC patients in Studies SHH4476g, SHH3925g, SHH4437g and SHH4610g

Table 1 (below) provides an overview of the studies and patient populations for which safety information will be provided in the NDA.

Is the proposed content of the SCS (Module 2) and ISS (Module 5) acceptable to the Agency?

Table 1  
Studies for which Safety Data Will Be Submitted in the NDA

Clinical Study	Study Phase	Indication	Vismodegib Exposure (N)
SHH4476g	II	Locally advanced or metastatic BCC	104

SHH3925g	I	Solid tumors	68
SHH4437g	Extension	Patients treated with vismodegib in a previous Genentech-sponsored Ph I or Ph II cancer study	Ongoing
SHH4429g	II	1 <sup>st</sup> -line colorectal cancer	98
SHH4489g	II	Ovarian cancer	52
SHH4318g	I	Pediatric medulloblastoma	1
SHH4610g	Schedule optimization	Cancer patients	63
SHH4683g	PK/mass balance	Healthy volunteers	24
SHH4433g	PK study	Healthy volunteers	3
SHH4871g	QT/QT <sub>c</sub> study	Healthy volunteers	20
SHH4811g	Expanded access	Locally advanced or metastatic BCC	38
NCI-CTEP #8395	Food effect study	Cancer patients	29
Other active studies not filed to IND 74, 573*			> 300

\* See Table 23 in the pre-meeting package for details on other studies

**Discussion:**

**The FDA clarified that the dataset from study 4489 can be submitted individually. However, the integrated safety analyses should include the safety data of those patients as pooled analyses and separately for each. The sponsor proposed format for ISSCIS and ISS is acceptable.**

5. Does the Agency agree that the proposed analyses and presentation of data proposed for the Summary of Clinical Efficacy (Module 2) fulfill the requirements for an Integrated Summary of Efficacy (see [Section 7.5](#))?

**FDA Response:**

Yes

**Clinical Pharmacology:**

6. Does the Agency agree that the clinical pharmacology program is sufficient to support the NDA for the proposed indication?

**FDA Response:**

**In addition to the clinical pharmacology studies you intend to submit in your anticipated NDA, we encourage you to also include the final clinical study reports and results for the DDI Study SHH4593g, food effect Study CTEP#8395 and the renal and hepatic studies in the NDA submission at the time of filing. This will be important for labeling and for safe and effective use of vismodegib.**

Sponsor Response:

Genentech acknowledges the importance of these three clinical pharmacology studies (renal and hepatic impairment are included in one study) for labeling purposes and all efforts are being made to complete these studies as quickly as possible. However, these are complex studies which enroll cancer patients rather than healthy volunteers, therefore the final clinical study reports will not be completed by the time of NDA filing.

Enrollment is ongoing for the DDI Study SHH4593g and for the food effect Study CTEP#8395g; a synoptic report will be included in the NDA submission, which will include results from the 29 of 48 patients who have completed the food effect study. Final study reports will be provided to the Agency at the time of completion of these two studies. The combined renal and hepatic impairment study design and planning was initiated after completion of the human mass balance study and feedback from the Agency in 2010; the protocol will be submitted to the Agency for review in August 2011. In the NDA, we will submit all relevant and available information on the potential for intrinsic and extrinsic factors to influence the exposure of vismodegib, including a population-PK analysis, which will explore the impact of creatinine clearance on vismodegib exposure.

Are there any specific analyses that the Agency would like included in the NDA to help facilitate review?

**FDA Response 5/11/11:**

- **You may include in the NDA the analyses of the effect of covariates (e.g., age, gender, race, ...etc) and the exposure-response relationships with respect to efficacy and safety.**
- **Please submit in your NDA the following datasets to support the population analysis:**
  - **All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
  - **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).**
  - **A model development decision tree and/or table which gives an overview of modeling steps.**

**For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**

**Discussion:**

**The sponsor concurs.**

- a. Has Genentech adequately addressed the Agency's previous questions and comments regarding the clinical pharmacology program (see [Section 5.3](#))?

**FDA Response:**

**Yes.**

Sponsor Response:

Genentech thanks the Agency for the thorough review of our responses to the previous questions and comments regarding the clinical pharmacology program.

**Nonclinical Pharmacology and Toxicology:**

7. Does the Agency agree that the nonclinical pharmacology and toxicology programs are sufficient to support the NDA for the proposed indication?

**FDA Response:**

**You will need to complete carcinogenicity studies for locally advanced BCC.**

Sponsor Response:

Genentech plans to initiate a SPA with CDER's executive carcinogenicity assessment committee prior to approval and to complete the assessment post-approval.

Is this acceptable to the Agency?

**Discussion:**

**If NDA is otherwise fileable, the Sponsor's proposal is acceptable.**

**Safety Update:**

8. Study SHH4476g has 51 patients who remained on treatment as of the 26 November 2010 data cutoff. Assuming priority review is granted, Genentech proposes to submit the required safety update for ongoing Studies SHH4476g and SHH4437g within 90 days post submission. Does the Agency agree with the content and timing of the safety update (see [Section 7.9](#))?

**FDA Response:**

**If a priority review is granted, your proposal is acceptable.**

(b) (4)



(b) (4)

c. Does the Agency agree with the proposed pregnancy pharmacovigilance program?

**FDA Response:**



(b) (4)

**NDA Contents:**

10. Regarding the proposed contents of the NDA (see [Section 7](#) for details):

- a. Does the Agency agree with the proposed plan for submitting patient narratives?

**FDA Response:**

**Yes, however, we may request additional narratives during the review process.**

Sponsor Response:

Genentech acknowledges the Agency's comment.

- b. Does the Agency agree with the proposed submission of Case Report Forms (CRFs) and Case Report Tabulations (CRTs)?

**FDA Response:**

**No. We could not find this information in your briefing package. Please refer to CSR§314.50(f) for the requirements regarding CRFs and CRTs in a NDA.**

**Sponsor Clarification Request:**

We acknowledge the Agency's response and have referred to *CFR§314.50(f)* which states that the Sponsor is required to submit all data from all controlled studies, earliest clinical pharmacology studies, and safety data from all other clinical studies unless the Agency agrees that particular tabulations are not pertinent to the review.

Genentech has proposed to not include datasets for the following studies in the NDA:

- SHH4318g, a single patient Phase I pediatric study in medulloblastoma
- SHH4429g, a Phase II controlled study in first line metastatic colorectal cancer patients treated with FOLFOX + Bevacizumab or FOLFIRI + Bevacizumab +/- vismodegib/placebo.
- SHH4811g, an ongoing expanded access study in advanced BCC patients.
- All ongoing NCI-CTEP studies and ISTs

Genentech has proposed to include selected datasets for the following studies in the NDA:

- SHH4437g, an ongoing rollover study in cancer patients. All BCC patients from this study will be included in the ISS datasets, standalone datasets from this study will not be provided
- SHH4610g, a dose scheduling Phase I PK study in cancer patients. The PK datasets will be provided and data from one aBCC patient will be included in the ISS datasets.
- SHH4683, a Phase I PK mass balance study in healthy volunteers. PK datasets only will be provided from this study.
- SHH4433g, a Phase I PK healthy volunteer study to characterize single dose PK. PK datasets only will be provided for this study.

Genentech proposes to submit the following SAS® XPT datasets in CDISC SDTM and AdAM format unless noted otherwise:

- Complete datasets for all patients in the pivotal and Phase I studies in aBCC patients, Studies SHH4476g and SHH3925g
- Pooled safety datasets (ISS) for aBCC patients in Studies SHH4476g, SHH3925g, SHH4437g and SHH4610g
- Complete datasets for the Phase II study in ovarian cancer patients, SHH4489g
- PK datasets from Studies SHH4433g, SHH4610g, and SHH4683g
- Population PK dataset(s) in (non-SDTM) XPT format, which includes combined data from Studies SHH4476g, SHH3925g, SHH4433g, SHH4610g, and SHH4683g
- PK exposure–response analysis dataset(s) for efficacy in (non-SDTM) XPT format, which will include data from Study SHH4476g
- PK exposure–response analysis dataset(s) for safety in (non-SDTM) XPT format, which will include combined data from Studies SHH4476g and SHH3925g
- Complete datasets from SHH4871g, which will include centrally assessed ECG and PK data

As described in Table 22 of the pre-meeting package, CRFs from all patients in the following studies will be included in the submission: SHH4476g, SHH3925g, SHH4437g, SHH4318g, SHH4610g, SHH4429g, SHH4489g, SHH4683g, SHH4871g, and SHH4433g.

Supporting documentation describing the dataset structures and the variables will be submitted in NDA. Annotated CRFs will be provided for all studies providing datasets that have data captured from CRFs.

SAS® programs used to create the derived datasets from raw datasets used in the primary and key secondary efficacy analyses for SHH4476g will be provided. SAS® programs used for the primary and key secondary efficacy analyses for SHH4476g will also be provided.

The STDM dataset format for the pivotal study SHH4476g is provided in Appendix 10.8 of the pre-meeting package.

It should be noted that a test submission of SDTM data from the SHH4610g study was provided to Dhananjay Chhatre at the Office of Business Informatics in April 2011.

Does the Agency consider the proposal for the datasets, CRFs, CRTs, and programs to be included in the NDA to be acceptable?

**Discussion:**

**Yes**

- c. Does the Agency agree with the proposed contents, structure, and format of the datasets?

**FDA Response:**

**In general, your proposal appears appropriate. Please refer to Guidance for Industry Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>**

- d. Does the Agency agree with the proposed submission of statistical programs?

**FDA Response:**

**Yes.**

- e. Does the Agency agree with the proposed format for submission of patient photographs?

**FDA Response:**

**Please clarify in what format you propose to submit patient photographs.**

**Sponsor Clarification Request:**

The photos will be submitted in PDF format in two resolutions. First, a proof-sheet series of medium resolution thumbnail images will allow review of all imaging for a particular patient visit. Second, the user may click on successive visit bookmarks to rapidly gain an overview of lesion appearance over the treatment period. By clicking on any image, a high resolution version of the selected image is displayed for detailed review.

Top level access to the images is from the "Medical Imaging" bookmark in the patient CRF.

Is this acceptable to the Agency?

**Discussion:**

Yes

- f. Does the Agency agree with the proposed format for submission of radiographic images?

**FDA Response:**

No.

**Sponsor Clarification Request:**

Could the Agency please clarify whether they will require the submission of radiographic images? If yes, could the Agency please clarify what format is acceptable?

**Discussion:**

No

- g. Does the Agency have other comments on the proposed contents of the NDA?

**FDA Response:**

No

**Regulatory:**

11. Does the Agency agree that the proposed NDA based on Study SHH4476g provides evidence of significant clinical benefit to this patient population with a high unmet medical need in the absence of other treatment options, and should qualify for priority review?

**FDA Response:**

**The decision whether to grant priority review is made at the time of NDA filing.**

12. 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:**

**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:**

**We will inform you once a determination is made.**

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

**4.0 ACTION ITEMS**

**5.0 ATTACHMENTS AND HANDOUTS**

*{See appended electronic signature page}*

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Ke Liu, M.D., PhD.  
Clinical Team Leader

*{See appended electronic signature page}*

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Yolanda G. Adkins, R.N., MSHA RPM  
Regulatory Project Manager

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/s/  
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KE LIU  
05/16/2011



IND 074573

**MEETING MINUTES**

Genentech, Inc.  
Attention: Mary B. Sliwowski, Ph.D.  
Vice President, Pharma Technical Regulatory  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Sliwowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0449.

We also refer to the meeting between representatives of your firm and the FDA on May 10, 2011. The purpose of the meeting was to obtain feedback from the Agency on CMC pre-NDA questions prior to submission of the NDA.

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

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA, CMC

**Meeting Date and Time:** May 10, 2011 10:00 – 11:00 AM, EDT  
**Meeting Location:** FDA White Oak, Building 22 Room 1417

**Application Number:** IND 074573  
**Product Name:** GDC-0449  
**Indication:** proposed as treatment of patients with metastatic basal cell carcinoma (BCC); (proposed) as treatment of patients with locally advanced BCC [REDACTED] (b) (4)

**Sponsor Name:** Genentech, Inc.

**Meeting Chair:** Sarah Pope Miksinski, Ph.D.  
**Meeting Recorder:** Tu-Van Le Lambert, M.S.

**FDA ATTENDEES**

Sarah Pope Miksinski, Ph.D., Branch Chief, Division of New Drug Quality Assessment I (DNDQAI), Office of New Drug Quality Assessment (ONDQA)  
Anne Marie Russell, Ph.D., Product Quality Reviewer, DNDQAI, ONDQA  
Haleh Saber, Ph.D., Supervisory Pharmacologist, Division of Hematology Products (DHP), Office of Oncology Drug Products (OODP)  
Wei Chen, Ph.D., Pharmacologist, DHP, OODP  
Tu-Van Le Lambert, M.S. – Product Quality Regulatory Project Manager, ONDQA

**SPONSOR ATTENDEES**

Nirdosh Jagota, Ph.D., Senior Director, Pharma Technical Regulatory, Genentech  
Thirunellai Venkateshwaran, Ph.D., Director, Pharma Technical Regulatory, Genentech  
Greg Gallegos, M.B.A., Senior Manager, Pharma Technical Regulatory, Genentech  
Ashraf Ahmed, Product Manager, Pharma Technical Regulatory, Genentech  
Bernd A Kraemer Ph.D., Head of Small Molecule Development Product Quality, Genentech  
David Askin, Ph.D., Associate Director, Small Molecule Pharmaceutical Sciences, Genentech  
Remy Angelaud, Ph.D., Senior Scientist, Small Molecule Pharmaceutical Sciences, Genentech  
Larry Wigman, Ph.D., Senior Scientist, Small Molecule Pharmaceutical Sciences, Genentech  
Minli Xie, Ph.D., Senior Scientist, Small Molecule Pharmaceutical Sciences, Genentech (on phone)  
Yong Cui, Ph.D., Scientist, Small Molecule Pharmaceutical Sciences, Genentech (on phone)  
Rick Graham, Ph.D., Clinical Pharmacologist, Pharmacology Sub-Team Leader, Genentech  
Stephen Gomez, Ph.D., Senior Manager, Product Quality & Occupational Toxicology, Genentech  
Kenjie Amemiya, Ph.D., Associate Director, Toxicology, Safety Assessment, Genentech

(b) (6)

## 1.0 BACKGROUND

The Sponsor has completed the Phase II pivotal study (SHH4476g) entitled, "A pivotal phase II multicenter, single-arm, two cohort trial evaluating the efficacy and safety of GDC-0449 in patients with advanced Basal Cell Carcinoma (aBCC)" to support the submission of an NDA for the proposed indications. The Sponsor requests feedback from the Agency on CMC aspects of the data to be submitted to the NDA.

## 2. DISCUSSION

Preliminary responses from the Agency were sent on May 9, 2011. Based on these preliminary responses, the Sponsor requested further discussion of Questions 1 and 4. These questions are included in the discussion below. Questions provided by the Sponsor are ***Bold Italics***, FDA Responses provided in preliminary comments are in Regular, discussion items during the meeting are in *Italics*.

### 2.1. Pharmacology/Toxicology

#### QUESTION 1

*A comprehensive assessment of potential genotoxic impurities in the commercial API process was performed. This includes in silico evaluation, an Ames testing strategy, purging studies, a chemical reactivity assessment, and analytical testing. Based on this assessment as well as analytical testing of all recent lots of the GDC-0449 API made by the commercial manufacturing process, Genentech has determined that any risk related to presence of potential genotoxic impurities is extremely low. Consequently, no genotoxic impurity specifications on the API are proposed. Does the Agency agree with our assessment and conclusions?*

#### Agency Response

No,

(b) (4)

See our response to the nonclinical question submitted to DDOP for the meeting of May 11, 2011, regarding the need to conduct carcinogenicity studies for the proposed patient population of locally advanced BCC.

#### Discussion

*The Sponsor summarized their strategy for assessing genotoxic potential of the impurities (see below, Sponsor's Summary of Genotoxic Impurities Strategy.) The Agency stated*

that the Sponsor's proposal for the three impurities, (b) (4) is acceptable. The Sponsor's approach for the five impurities, (b) (4) (b) (4) is reasonable. However, the Agency stated that the decision on these five impurities will be a review issue and recommended that supporting data be provided with the NDA. The Sponsor acknowledged these responses.

*Sponsor's Summary of Genotoxic Impurities Strategy*



**2.2. Chemistry, Manufacturing and Controls – Biopharmaceutics**

**QUESTION 2**

*GDC-0449 is formulated as an immediate-release hard capsule. Based on the solubility and permeability data, it has been designated as a BCS Class 2 compound. The dissolution method utilizes a standard approach and has been demonstrated to be discriminating. Does the Agency agree that the dissolution method and proposed specification provide sufficient control for commercial manufacturing?*

**Agency Response**

The method appears reasonable. However, the Agency recommends that you consider adjusting the Q value to (b) (4). Final determination on acceptability will be made during the review of the NDA.

**Discussion**

*The Sponsor accepted the preliminary responses and no further discussion was needed.*

**QUESTION 3**

*Based on the relationship of particle size to in vitro dissolution, does the Agency agree that the proposed particle size acceptance criterion of (b) (4) is acceptable for registration?*

**Agency Response**

Given that your API is a BCS class II drug and poorly soluble in (b) (4) acceptance criterion for particle size distribution is needed to control the manufacturing and performance of your drug product.



**Discussion**

*The Sponsor accepted the preliminary responses and no further discussion was needed.*

**2.3. Chemistry, Manufacturing and Controls**

**QUESTION 4**

*Given the scale and equipment changes made between the Drug Product registration lots and the proposed commercial-scale (scale-up) lots, does the Agency agree that the analytical comparability data presented are acceptable to qualify these changes?*

**Agency Response**

Insufficient information was provided in your meeting package to address this question.

In order to provide a response to this question, the following should be addressed:

- Confirm if a site change was made.
- In addition to the dissolution and content uniformity data submitted, address the impact of equipment, scale and process changes on release specifications and stability, including the primary stability data intended to support the NDA.
- Provide a comprehensive summary of changes and comparability analysis.
- Identify the stability batches (primary and supportive) intended for inclusion in the NDA, describe the available data for each batch and provide test results or summarize the stability program findings to date.

**Discussion**

- *The Sponsor described the changes between the registration and commercial scale batches of their drug product and confirmed that there was no site change. They provided a description of the analytical comparability data between the registration and commercial scale batches to justify comparability to be used in the NDA submission. The Sponsor asked whether the information provided allows the Agency to agree with the proposed comparability data package in the meeting package.*
- *The Agency stated that there was insufficient applicable data in the meeting background package and their meeting slide presentation to provide a response to this question – for example no drug product specifications, batch data or stability data were provided. The Agency stated that the sponsor appeared to be considering submitting three registration batches, which were not manufactured using the commercial process, as primary stability data to support a determination of a drug product expiry. The Agency advised that bridging these registration batches to a single commercial batch using a comparability approach may be complicated due to the manufacturing changes between registration and commercial process (equipment, scale, etc.) The Agency stated that sufficient stability data to support a commercially viable expiry should be submitted in the original NDA and recommended at least 12 months of stability data on three commercial batches. The Sponsor reaffirmed their intention to demonstrate that their registration and commercial batches are adequately determined to be comparable. The Agency stated that the acceptability of the comparability will be a review issue.*
- *The Agency reminded the Sponsor that, at the time of NDA submission, sufficient stability data to support a commercially viable expiry is recommended; lack of this data or supportive comparability data could be considered a filing issue according to 21<sup>st</sup> century review.*
- *The Sponsor asked whether the registration stability batch could be acceptable if it complies with ICH. The Agency responded that while it could be acceptable depending on comparability, insufficient information was provided to determine if the proposed registration batches were comparable to the commercial batches. Final determination of comparability is a review issue and will be dependent, in part, on the changes made in the manufacturing between the registration and commercial process.*
- *The Sponsor asked whether the Agency would consider the historical stability for the drug product when making a stability assessment for the commercial product. The Agency replied that while this information is reassuring, it will be considered supportive, and adequate primary stability data should be included in the application to support the stability of the drug product.*
- *When asked whether comparability between the registration and the commercial batches of the drug product will be based on commercial batch stability data, the Agency responded that stability of the commercial batch will be a part of the information considered in determining the comparability between registration and commercial batches.*

- *The Agency suggested that the Sponsor has the option of another meeting or an amendment if they wish to pursue this issue further. The Sponsor acknowledged this advice and stated they would consider this advice. They advised that they intend to submit the NDA in August 2011.*

### **QUESTION 5**

***Does the Agency agree with the proposal to provide one (1) executed Drug Product batch record from the three (3) primary stability (registration) lots as part of the NDA submission?***

#### **Agency Response**

No. Per 21 CFR 314.50 “Content and format of an application”, include the batch production record for each batch of drug product used to conduct a primary stability study.

#### **Discussion**

*The Sponsor accepted the preliminary responses and no further discussion was needed.*

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues requiring further discussion were identified during the meeting.

### **4.0 ACTION ITEMS**

No action items were identified during the meeting.

### **6.0 ATTACHMENTS AND HANDOUTS**

Presentation: Vismodegib (GDC-0449) IND 074573 Pre-NDA Meeting: Topics For Further Discussion



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**Vismodegib (GDC-0449) IND 074573**  
**Pre-NDA Meeting: Topics For Further Discussion**  
**May 10, 2011**

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# Question 1: Genotoxic Impurities

# Summary of Genotoxic Impurities Strategy



(b) (4)

**Does the Agency agree with this approach?**

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## **Question 4: Drug Product Scale and Equipment Changes**

## Summary of Changes between Registration and Commercial Scale (scale-up) batches

- No site changes during development, registration and scale-up manufacturing;

(b) (4)

- Equipment of the same design and operating principles; same equipment manufacturer



## **Analytical Comparability Data between Registration and Commercial Scale (scale-up) batches included in NDA**

- Release data from 3 registration batches and a minimum of 3 scale-up batches
- Dissolution profile comparison for 3 registration batches and a minimum of 3 scale-up batches
- Stability Data
  - 3 Primary Stability Batches: 18 months Long-Term stability (30°C/65%RH), 6 months Accelerated stability (40°C/75%RH)
  - 1 Bridging (Commercial Scale) Stability Batch: 3 months Long-Term Stability (30°C/65%RH) and Accelerated stability (40°C/75%RH)

**Does the Agency agree with our proposed comparability data package?**



*We Innovate Healthcare*

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/s/  
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SARAH P MIKSINSKI  
06/01/2011



IND 074573

**MEETING PRELIMINARY COMMENTS**

Genentech, Inc.

Attention: Mary B. Sliwowski, Ph.D.  
Vice President, Pharma Technical Regulatory

1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Sliwowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0449.

We also refer to your January 21, 2011, correspondence, received January 24, 2011, requesting a meeting to discuss input from the Agency on CMC pre-NDA questions prior to submission of the NDA.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **Tuesday, May 10, 2011 10:00 – 11:00 AM, EDT, at FDA White Oak** between **Genentech, Inc.** and the **Office of New Drug Quality Assessment**. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

### **QUESTION 1**

**A comprehensive assessment of potential genotoxic impurities in the commercial API process was performed. This includes in silico evaluation, an Ames testing strategy, purging studies, a chemical reactivity assessment, and analytical testing. Based on this assessment as well as analytical testing of all recent lots of the GDC-0449 API made by the commercial manufacturing process, Genentech has determined that any risk related to presence of potential genotoxic impurities is extremely low. Consequently, no genotoxic impurity specifications on the API are proposed. Does the Agency agree with our assessment and conclusions?**

#### **Agency Response**

No,

(b) (4)

See our response to the nonclinical question submitted to DDOP for the meeting of May 11, 2011, regarding the need to conduct carcinogenicity studies for the proposed patient population of locally advanced BCC.

### **QUESTION 2**

**GDC-0449 is formulated as an immediate-release hard capsule. Based on the solubility and permeability data, it has been designated as a BCS Class 2 compound. The dissolution method utilizes a standard approach and has been demonstrated to be discriminating. Does the Agency agree that the dissolution method and proposed specification provide sufficient control for commercial manufacturing?**

#### **Agency Response**

The method appears reasonable. However, the Agency recommends that you consider adjusting the Q value to (b) (4). Final determination on acceptability will be made during the review of the NDA.

### **QUESTION 3**

**Based on the relationship of particle size to in vitro dissolution, does the Agency agree that the proposed particle size acceptance criterion of [REDACTED] (b) (4) is acceptable for registration?**

#### **Agency Response**

Given that your API is a BCS class II drug and poorly soluble [REDACTED] (b) (4) acceptance criterion for particle size distribution is needed to control the manufacturing and performance of your drug product.

(b) (4)

(b) (4)

### **QUESTION 4**

**Given the scale and equipment changes made between the Drug Product registration lots and the proposed commercial-scale (scale-up) lots, does the Agency agree that the analytical comparability data presented are acceptable to qualify these changes?**

#### **Agency Response**

Insufficient information was provided in your meeting package to address this question.

In order to provide a response to this question, the following should be addressed:

- Confirm if a site change was made.
- In addition to the dissolution and content uniformity data submitted, address the impact of equipment, scale and process changes on release specifications and stability, including the primary stability data intended to support the NDA.
- Provide a comprehensive summary of changes and comparability analysis.
- Identify the stability batches (primary and supportive) intended for inclusion in the NDA, describe the available data for each batch and provide test results or summarize the stability program findings to date.

**QUESTION 5**

**5. Does the Agency agree with the proposal to provide one (1) executed Drug Product batch record from the three (3) primary stability (registration) lots as part of the NDA submission?**

**Agency Response**

No. Per 21 CFR 314.50 “Content and format of an application”, include the batch production record for each batch of drug product used to conduct a primary stability study.

=====

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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SARAH P MIKSINSKI  
05/09/2011

**Type B Meeting (January 25, 2011) – List of Questions  
GDC-0449 (Hedgehog Pathway Inhibitor)  
IND 74,573**

**Nonclinical**

- 1) Studies that have been completed or planned include an ICH genotoxicity battery, general toxicity studies up to 26 weeks in duration in rats and dogs, a dedicated cardiovascular safety pharmacology study in dogs, an embryo-fetal development study in rats, a fertility study in rats, and carcinogenicity studies (as described in Section 3.2 and Question 2 below).

Does the Agency agree that the nonclinical toxicity studies that have been completed to date and those that are planned are sufficient to support the proposed indication?

**FDA Response:**

**Yes, we concur that studies conducted and planned are sufficient.**

**However, the adequacy of the studies will be made after review of the data.**

- 2) Does the Agency agree with the plan to complete carcinogenicity evaluations of GDC-0449 consisting of a 2-year study in Sprague Dawley rats and a 6-month study in Tg.rasH2 mice to support the proposed indication?

**FDA Response:**

**Yes, we concur.**

**To facilitate the review process, at least 30 days prior to submission of the study protocol, notify the Agency in writing that a carcinogenicity protocol will be arriving. Mark the submission as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT. It also should be clearly marked as a carcinogenicity study protocol.**

**See "Guidance for Industry; Carcinogenicity Study Protocol Submissions."**

- 3) Does the Agency agree that a peri-/post-natal development study is not required to support the proposed indication in an adult patient population because of the known developmental liabilities of GDC-0449, (b) (4)

**FDA Response:**

**Based on the summary information provided, indicating that GDC-0449 is teratogenic, we concur that a peri-/post-natal development study will not be needed. A final decision will be made after review of the development toxicity study.**

**Clinical**

(b) (4)

**FDA Response:**

(b) (4)

5) Is the proposed target patient population adequately defined per the study eligibility criteria?

**FDA Response:**

**No.**

(b) (4)

6) Does the agency agree with the proposed cross-over study design? Is the placebo-control plus best supportive care appropriate to assess the efficacy of GDC-0449 in this patient population?

**FDA Response:**

**a. No,** (b) (4)

(b) (4)

**b. Your proposed placebo-control plus best supportive care appears to be reasonable to assess the efficacy of GDC-0449 in this patient population.**

- 7) Does the Agency agree the selected dose and dosing regimen of 150 mg daily for 24 weeks is appropriate for the proposed indication?

**FDA Response:**

**The proposed daily GDC-0449 150 mg oral dose may not be optimized for efficacy. In GDC-0449 phase 1 trials, there were no DLT's, and no dose response was observed because of the saturable absorption. In terms of the regimen, please provide your rationale to support the proposed 24 week treatment duration. Also, please address our previous clinical pharmacology comments:**

- i. (Refer to the April 28, 2008 End-of-Phase 1 meeting minutes.) Do you have plans for developing an IV formulation or investigate different oral dosing schedules given the long half-life, saturable absorption, and failure to reach the MTD?**
- ii. (Refer to the July 9, 2010 Type C meeting minutes.) We recommend you assess dose proportionality below the proposed clinical dose of 150 mg daily for dose adjustment recommendations.**

- 8) Does the Agency agree with the proposed safety monitoring plan?

**FDA Response:**

**Yes. However, in most clinical oncology protocols, the dose of study drug is reduced if treatment is restarted after a dose interruption. Please justify your proposal to restart treatment at the same dose and schedule.**

- 9) Does the Agency agree that the primary endpoint of BCC50 response at Week 25, defined as a 50% reduction in the number of clinically apparent BCCs at Week 25 compared with baseline, is an appropriate endpoint for demonstration of clinical benefit in the proposed patient population?
- a. Does the Agency agree with the proposed tumor assessment for the primary endpoint?

**FDA Response:**

- i. **The proposed endpoint of 50% reduction in BCCs in this syndrome may be appropriate depending on the risk/benefit calculus of this particular drug product. However, evidence of histologic clearance will be necessary. While it may not be practical to biopsy every cleared lesion, a representative number of clinically cleared areas should be biopsied. We would suggest at least one on the face and one on the back/extremities. You should map all the lesions at baseline to make sure you identify which lesions are clinically clear. You should specify your technique used for mapping.**
- ii. **For a lesion to be considered a complete response, the area where the lesion was located must remain completely normal in appearance until the completion of the primary endpoint evaluation. In addition there must be no new lesions or clear progression of existing lesions.**
- iii. **The Statistical Analysis Plan must specify whether all BCC lesions are to be counted. Please address how you plan to handle patients whose BCCs may be too numerous to count or who have lesions surgically removed.**
- b. Would a difference in the BCC50 response at Week 25 that is significantly greater than 40% in the GDC-0449 arm relative to the placebo arm be considered a clinically meaningful benefit (b) (4)?

**FDA Response:**

**For drug approval, you would need to demonstrate not only a clinically meaningful response rate, but also that the responses obtained were durable. Whether this endpoint will translate into a clinical benefit will be a review issue.**

10. Does the Agency agree that the proposed sample size and statistical analysis plan will enable inclusion of both the primary and key secondary endpoint in the label?



(b) (4)

**FDA Response:**

**No.**

(b) (4)

(b) (4)

**FDA Response:**

**No.** (b) (4)

**Classification of GDC-0449**

12. Does the Agency support an application for Orphan Drug Designation for GDC-0449 (b) (4)

**FDA Response:**

(b) (4)

the disease or condition in the request for orphan drug designation would be treatment of BCC. GDC-0449 does not qualify for orphan drug designation for treatment of BCC as this is not a rare disease or condition.

**Additional Comments:**

1. Perform a fertility analysis after 1<sup>st</sup> 24 weeks of treatment.
2. During GDC-0449 drug development, you should conduct an *in vitro* study to determine if GDC-0449 is a P-glycoprotein substrate; we refer you to the FDA meeting minutes from the April 28, 2008 End-of-Phase 1 meeting.

**3. Regarding protocol SHH4949g:**

- a. GDC-0449 pharmacokinetics should also be characterized during the Part when patients are taking the active medication (e.g. within Cohort 1 during Part1 or within Cohort 2 during Part 2).**
- b. The alpha 1-acid glycoprotein plasma concentration sampling time points should be listed in the protocol and the study flowchart.**
- c. Medications that are CYP 3A4 inducers or inhibitors should also be excluded or used with extreme caution in the study.**

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/s/  
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JAMILA MWIDAU  
01/21/2011



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Oncology Drug Products  
Division of Drug Oncology Products**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: July 6, 2010**

<b>To:</b> Bao Truong Regulatory Scientist, Clinical Regulatory	<b>From:</b> Alberta E. Davis-Warren Regulatory Health Project Manager Alberta.Davis-Warren@fda.hhs.gov
<b>Company:</b> Genentech, Inc.	Division of Drug Oncology Products
<b>Fax number:</b> truong.bao.gene.com	<b>Fax number:</b> 301-796-9845
<b>Phone number:</b> 650-225-7635	<b>Phone number:</b> 301-796-3908
<b>Subject:</b> Preliminary responses for July 9, 2010 teleconference	

**Total no. of pages including cover:** 6

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Dear Ms. Truong,

The attached consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for between you and the Division of Drug Oncology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting. If you choose to cancel the meeting, this document will represent the official record. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or change the format of the meeting (e.g., from face to face to telecon). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan/the purpose of the meeting/to the

questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

## **PRELIMINARY RESPONSES for July 9, 2010 Type C teleconference with Genentech, Inc. 3:30-4:30 PM EDT (IND 074573 GDC-0449)**

### **SPECIFIC QUESTIONS**

#### **Nonclinical**

1. Does the Agency agree that the nonclinical toxicology program is sufficient to support the registration of GDC-0449? Specifically, does the Agency agree with the plan not to conduct carcinogenicity, fertility, peri/post-natal development, or additional embryofetal development toxicity studies with GDC-0449 for the proposed indication of metastatic or locally advanced basal cell carcinoma?

**FDA response: You will need to justify why carcinogenicity studies are not needed based on the life expectancy of patients with locally advanced basal cell carcinoma. We agree that fertility and peri/post-natal developmental studies are not needed. Based on the limited information provided for the pilot embryofetal developmental study in rats showing embryofetal mortality or malformations, a pivotal developmental study may not be needed. However, the final decision will be made following review of data submitted with your NDA. You will need to provide the animal exposure data for Embryofetal Developmental Study in Rats (Study 3036R09), and compare those to the human exposure at the recommended therapeutic dose. The pharmacokinetic data in rats could be based on other studies conducted at the same dose levels and schedule.**

#### **Clinical Pharmacology**

2. Does the Agency agree that the overall clinical pharmacology program is sufficient to support registration of GDC-0449?

**FDA response: No, see responses to 3 – 7 below. In addition, we recommend you assess GDC-0449 dose proportionality below the proposed clinical dose of 150 mg daily. These data may be useful when making potential dose adjustment decisions.**

3. Does the Agency agree with the proposed gated approach for DDI assessment with GDC-0449 as a perpetrator via CYP inhibition?

**FDA response: Yes, the proposed plans appear acceptable. PK blood samples should also be obtained at pre-dose on Days 1 and 8. Additionally, the renal function inclusion criteria should be modified to include patients with SCr  $\leq 1.5 \times$  ULN.**

4. Does the Agency agree with the rationale for not conducting clinical studies of CYP inhibition/induction (i.e., GDC-0449 as victim) given the low likelihood of such interactions?

**FDA response: This is a review issue. The data you submitted have not demonstrated that the contribution of the CYP enzymes to the overall elimination of GDC-0449 is not substantial. Please provide data of the extent of GDC-0449 metabolism and evaluate the importance of GDC-0449 metabolism based on the results from your in vitro and in vivo studies.**

5. Does the Agency agree with the proposed dedicated QT-interval study design in healthy volunteers (SHH4871g) and the statistical methods described within the protocol summary?

**FDA response:**

**We agree with your statistical design; however, we would like to make a comment about the sample size proposed in Arm C (treatment GDC-0449 arm). If the true mean difference between your study drug and placebo after baseline correction is 5 ms or smaller, your proposed sample size will be enough to rule out 20 ms; otherwise, you might need to consider increasing sample size in Arm C.**

6. Does the Agency agree that the ADME study (SHH4683g) results are sufficient to address the mass balance and absolute bioavailability of GDC-0449 in humans? Specifically, does the Agency agree that the mass balance findings to date are adequate to confirm that a renal impairment study is not required?

**FDA response: In general, your plans to address the mass balance and absolute bioavailability of GDC-0449 in humans appear acceptable. It appears that both renal and hepatic impairment studies will be necessary.**

7. Does the Agency agree with the hypotheses behind the current PK model and the analysis plan for modeling and simulation?

**FDA response: Yes, we agree. In order to explore exposure-response relationships for efficacy and safety in the confirmatory trial(s), you should collect sparse PK samples from all patients.**

**Additional Comments Regarding Study SHH4871g:**

- 1. The rationale for dose selection appears to be reasonable.**
- 2. ECG/PK sampling time points appear to be reasonable.**
- 3. We are okay with your statistical design. If the true mean difference between your study drug and placebo after baseline correction is 5 ms or smaller, your proposed sample size will be enough to rule out 20 ms; otherwise, you might need to consider increasing sample size in Arm C (treatment GDC-0449 arm).**

4. We have concerns about your plan to replace subjects who withdraw from the study. Subject replacement will violate the randomization principle. Efforts should be made to enroll and retain the subjects for the entire study period. If the reasons for withdrawal are related to the treatment, then replacing subjects could bias the results. In addition, having to adjust enrollment due to withdrawals during the trial may pose logistical problems and may affect the integrity of the trial. You might need to consider enrolling more subjects in terms of the anticipated dropout rate.
5. In most cases, a linear mixed effects modeling approach may be used to quantify the relationship between plasma concentrations (of the parent drug and/or metabolite(s)) and  $\Delta\Delta QTc$  (time-matched drug-placebo difference in  $QTc$  interval, baseline-adjusted). Based upon this relationship, the predicted population average  $\Delta\Delta QTc$  and its corresponding upper 95% 1-sided confidence interval bound may be computed at appropriate concentrations, eg, the mean maximum plasma concentrations under therapeutic and suprathreshold doses or other concentrations of interest. In addition to the above analysis, there may be merit in considering alternate dependent variables such as  $QTc$  or  $\Delta QTc$  (baseline-adjusted) to derive the  $\Delta\Delta QTc$  endpoint. We encourage the exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Therefore, diagnostic evaluation is expected as part of the application of the method recommended here. Additional exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).
6. We recommend that you incorporate the following elements into your assessment of the ECGs recorded during this study:
  - a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation
  - b. Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers
  - c. Review of ECGs from a particular subject should be performed by a single reader
  - d. Pre-specify the lead for interval measurements
  - e. Baseline and on-treatment ECGs should be based on the same lead
7. When you submit your 'thorough QT study' report, please include the following items:
  - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
  - b. Electronic copy of the study report
  - c. Electronic or hard copy of the clinical protocol
  - d. Electronic or hard copy of the Investigator's Brochure
  - e. Annotated CRF
  - f. A data definition file which describes the contents of the electronic data sets
  - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-74573	GI-1	GENENTECH INC	GDC-0449 (SYSTEMIC HEDGEHOG PATHWAY ANTA

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ALBERTA E DAVIS WARREN  
07/06/2010



IND 074573

**TREATMENT PROTOCOL  
ACKNOWLEDGEMENT**

Genentech, Inc.  
Attention: Bao-Tran Truong  
1 DNA Way  
South San Francisco, CA 94080

Dear Ms. Truong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0449 (Hedgehog Pathway Inhibitor).

We acknowledge our May 24, 2010 receipt, of your treatment protocol titled "SHH4811: A Single Arm Open Label Expanded Access Study of GDC-0449 in Patients with Locally Advanced or Metastatic Basal Cell Carcinoma," dated May 24, 2010.

Use of this investigational drug in humans, under this treatment protocol, may not be initiated until 30 days after the date of receipt shown above or on earlier notification by FDA, as per 21 CFR 312.305(d)(2)(ii). Therefore, unless we notify you otherwise, you may not initiate your proposed treatment protocol before June 24, 2010. If, within the 30-day period, we find that your submission is deficient under 21 CFR 312.42(b)(3), we will immediately notify you by telephone that the study may not proceed ("partial clinical hold"). In that event, it is understood that you will not proceed with the treatment use of this investigational drug until FDA notifies you that treatment use under this protocol may proceed.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that treatment with the investigational drug may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

We remind you that, under 21 CFR 312.8(a)(3), you may not charge for this investigational drug without prior written authorization from FDA.

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. 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, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-3908.

Sincerely,

*{See appended electronic signature page}*

Alberta E. Davis-Warren  
Regulatory Health Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-74573	ORIG-1	GENENTECH INC	GDC-0449 (SYSTEMIC HEDGEHOG PATHWAY ANTA

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/s/

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ALBERTA E DAVIS WARREN  
06/08/2010

DEPARTMENT OF REGULATORY AFFAIRS

1 DNA Way MS#242  
South San Francisco, CA 94080-4990  
(650) 225-1558  
FAX: (650) 467-3198

**HEALTH AUTHORITY CONTACT REPORT**

Reference: **IND 74,573**  
Product: GDC-0449  
Subject: FDA meeting  
Meeting Type: Type C face-to-face  
Meeting Purpose: Feedback on CMC plans to support Q2-2011 NDA  
Meeting Date: April 29, 2009

Agency Participants: Sarah Pope (CDER/OPS/ONDQA/DPAMS)  
Terrance Ocheltree (CDER/OPS/ONDQA/DPAMS)  
Debasis Ghosh (CDER/OPS/ONDQA/DPAMS)  
Grace McNally (CDER/OC/DMPQ)  
Deborah Mesmer (CDER/OPS/ONDQA/DPAMS)

Genentech Participants: Greg Gallegos, Lynne Krummen, Andrea Canavero  
(Regulatory CMC),  
David Stirling, Mark Reynolds, David Askin, Nik Chetwyn,  
Yong Cui, Minli Xie (Small Molecule Pharmaceutical  
Sciences),  
Kavita Mistry (Small Molecule Clinical Quality)

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***Executive Summary:***

Genentech (GNE) had an informative and successful meeting with the FDA. The FDA expressed they were pleased with the thoroughness of the Pre-Meeting Package (PMP) and indicated that it was an inter-disciplinary effort to review the PMP, which was interesting and challenging. Based on the preliminary FDA responses to the PMP questions, GNE indicated that further discussion was desired for the responses provided to API Questions 1, 3 and 5 in order for GNE to provide and receive some minor clarifications. All other FDA responses to the PMP questions were clear to GNE and were not discussed during the meeting.

**Meeting Minutes:**

**Question 1: (API) Does the Agency agree with Genentech's rationale and justification for the designation of compounds (b) (4) as the API starting materials for GDC-0449?**

**FDA Response:**

*Based on the information provided in the briefing document, FDA agrees that (b) (4) (b) (4) are acceptable starting materials. (b) (4) the level of impurity (b) (4) in the starting material (b) (4) and provide adequate control strategies, including purging studies, to limit the amount of the following impurities in the API:*

(b) (4)

*In addition, provide the acceptable 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 materials.*

**Discussion:**

- GNE agreed to (b) (4) the acceptance criteria for (b) (4) in the starting material (b) (4) specification.

(b) (4)

- FDA (Sarah Pope, SP) suggested the NDA process development section should communicate the understanding of how impurities are formed, how impurities (b) (4), and what changes impact impurity (b) (4)
- GNE provided clarification around change control strategies for Starting Materials. Genentech's supplier qualification program includes establishing quality agreements with each of the starting material suppliers that allow visibility and notification to manufacturing changes.

**Question 5: (API) Does the Agency agree with Genentech's strategy and approach to setting the commercial specification for API?**

***FDA Response:***

*The proposed strategy for setting the commercial specification is not adequate. When reporting impurities in the drug substance, follow ICHQ3A(R2). Report organic impurities as individual specified identified impurities, individual specified unidentified impurities, individual unspecified impurities, and total impurities. Justify all specifications using scientific rationale and historical batch data. In addition, include Residue on Ignition (USP<281>) as one of the critical attributes in Table 5.5.1-1. Adequacy will be determined at the time of NDA review.*

Discussion:

- GNE agrees that the impurity acceptance criteria for the API specification will be in alignment with ICH guidelines, process development understanding, and toxicology qualification at time of NDA filing.
- GNE clarified that *Residue on Ignition (USP<281>)* is already included as part of the API specification (b) (4) and the suitability of the method has been verified. FDA (DG) confirmed that ROI on the API specification was overlooked during the review of the PMP and that this comment is now addressed.

**Question 3: Does the Agency have any concerns with Genentech's proposed strategy for API process validation to support registration?**

***FDA Response:***

*Process validation involves an objective, scientific demonstration of process control so that batches of active pharmaceutical ingredients (APIs) or drug product consistently meet documented specifications. Process validation is a CGMP requirement for finished pharmaceuticals under 21 CFR §211.100(a) and 21 CFR §211.110(a) and for APIs under the Food Drug and Cosmetic Act. This requirement must be met before product is commercially distributed and then maintained during commercialization. The status of process validation is periodically assessed to assure ongoing state of control. Processes must be capable, maintained as stable, and assured by robust monitoring methods to verify the process is in control.*

*We do not approve process validation protocols and plans. During on site inspections, FDA field staff will evaluate validation protocols and studies.*

*We support your efforts to gain process understanding and use experimental design to study critical process parameters and critical quality attributes. A good understanding of the variables, both material attributes and processing parameters, in each unit operation that impact the API's or drug product's specifications and quality attributes, will enable you to generate a sound protocol(s) for the commercial scale performance qualification. For example, your protocol(s) should address the process performance criteria against which you will judge the success of your process validation study(ies). Protocols should also address the data and measurements to be collected, sampling plans, comparisons to be made between individual commercial runs included in the study(ies), and the scientific data analyses, including any statistical analyses, to be performed on all the data collected. A scientific rationale for the protocol design should be available.*

*Although the FDA does not approve validation protocols, the Office of Compliance will meet to discuss your validation program questions in greater detail at a meeting scheduled for this purpose and may request participation by the appropriate FDA district office. Submit your request for such a meeting to the Office of Compliance following the Guidance for Industry, Formal Meetings With Sponsors and Applicants for PDUFA Products. As you develop your validation program, please consider FDA's draft revisions to the Guidance to Industry, General Principles of Process Validation, published in November 2008.*

*In addition, you should consider the development of a Quality by Design (QbD) approach to mitigate risk during the process and to allow process flexibility while ensuring quality.*

Discussion:

- GNE thanked the FDA for their comments and for providing a mechanism to seek guidance on our process validation plans. GNE stated that they are looking to build elements of QbD into the GDC-0449 filing and to perform design of experiments (DOEs) to characterize the GDC-0449 process, identify critical process parameters and design space and would also like to identify a mechanism for gaining advice on ensuring adequate review of QbD elements that may be included in the NDA filing. FDA (Grace McNally, GM) stated that QbD elements incorporated in process validation will be reviewed during pre-approval inspection (PAI), however inspectors will defer to the reviewers for providing application guidance. FDA (Terrance Ocheltree, TO), stated that QbD is a grey area that covers both the compliance and review divisions.
- FDA (GM) expects process understanding, impurity formation and impurity removal to be communicated in filings. The inspection team will not be responsible for judging the conditions of approval, although it is currently not clear what elements of QbD an application should contain. FDA (TO) noted that the Review division will be looking for process understanding separate from process validation. Process validation does not show an understanding of design space. A submission should show a scientific understanding of the process and the number of batches included in a process validation is not significant.
- FDA (GM) stated the PMP package looks good and was pleased to see that GNE is applying QbD concepts. GM noted that the DOEs should include risk analyses to identify critical steps and to establish design space. GNE discussed that QbD elements, where they seemed warranted based on risk, would be incorporated but would not seek to create design space for each process step.
- GNE asked about how to obtain additional guidance from FDA regarding QbD issues, such as lessons learned from the pilot program. FDA (SP) stated that additional meetings with the Agency can be requested as necessary and that these types of meetings are usually helpful if the PMP is thorough.
- GNE clarified the GDC-0449 validation will follow a traditional approach but will include some elements of QbD understanding. The API and Drug Product processes include in-process controls (IPCs) at various stages, but no formal process analytical technology (PAT) will be included in the NDA submission.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 74,573

**MEETING MINUTES**

Genentech, Inc.  
Attention: Mary B. Sliwkowski, Ph.D.  
VP, Regulatory CMC and Information Systems  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Sliwkowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0449.

We also refer to the meeting between representatives of your firm and the FDA on April 29, 2009. The purpose of the meeting was to discuss questions from your meeting briefing package related to Chemistry, Manufacturing and Controls.

A copy of the official minutes of the meeting 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

<b>Sponsor Name:</b>	Genentech
<b>Application Number:</b>	IND 74,573
<b>Product Name:</b>	GDC-0449
<b>Meeting Requestor:</b>	Greg Gallegos, M.B.A. Senior Manager, Regulatory CMC, Genentech
<b>Meeting Type:</b>	Type C
<b>Meeting Category:</b>	Chemistry, Manufacturing and Controls (CMC) Guidance
<b>Meeting Date and Time:</b>	Wednesday, April 29, 2009 11:00 – 12:00 ET
<b>Meeting Location:</b>	Food and Drug Administration, White Oak Campus, Silver Spring, MD
<b>Received Briefing Package</b>	March 31, 2009
<b>Meeting Chair:</b>	Sarah Pope Miksinski, Ph.D.
<b>Meeting Recorder:</b>	Deborah Mesmer, M.S.

**FDA ATTENDEES:**

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of Pre-Marketing Assessment III:

Sarah Pope Miksinski, Ph.D. Branch Chief,  
Terrance Ocheltree, Ph.D., R. Ph. Pharmaceutical Assessment Lead (Acting)  
Debasis Ghosh, Ph.D., Review Chemist  
Deborah Mesmer, M.S. Regulatory Health Project Manager for Quality

Office of Compliance

Grace McNally, CSO, DMPQ/CMGB

**EXTERNAL ATTENDEES (GENENTECH):**

Lynne Krummen, Ph.D. Senior Director, Regulatory CMC  
Greg Gallegos, M.B.A. Senior Manager, Regulatory CMC  
Andrea Canavero, M.B.A. Senior Associate, Regulatory CMC  
David Stirling, Senior Director, Small Molecule Pharmaceutical Sciences  
David Askin, Ph.D. Associate Director, Small Molecule Pharmaceutical Sciences  
Mark Reynolds, Ph.D., Senior Scientist, Small Molecule Pharmaceutical Sciences,  
Nik Chetwyn, Ph.D. Senior Scientist, Small Molecule Pharmaceutical Sciences  
Minli Xie, Ph.D., Senior Scientist, Small Molecule Pharmaceutics  
Yong Cui, Ph.D. Scientist, Small Molecule Pharmaceutics  
Kavita Mistry, Ph.D. Senior Manager, Small Molecule Clinical Quality

**1.0 BACKGROUND**

Hedgehog Pathway Inhibitor, GDC-0449, is being developed by Genentech as a treatment for basal cell carcinoma. Genentech submitted a Type C, CMC meeting request dated February 11, 2009, received February 12, 2009, seeking FDA's guidance on the proposed CMC development plans for GDC-0449 to support an NDA in 2Q11. A face-to-face meeting was granted on March 5, 2009, scheduled to be held on April 29, 2009. The meeting briefing package dated March 30, 2009, was received on March 31, 2009. Preliminary responses to the questions contained in the meeting briefing package were archived in the administrative file and shared with Genentech on April 28, 2009. Based on FDA's preliminary responses, Genentech focused the meeting agenda to questions 1, 3 and 5 for discussion during the face-to-face meeting as scheduled. The minutes of the discussion and the slide pack that was distributed at the meeting but not presented, are recorded below.

**2.0 SPONSOR QUESTIONS, FDA PRELIMINARY RESPONSES. AND MEETING DISCUSSION****2.1 DRUG SUBSTANCE**

**Question 1:** Does the Agency agree with Genentech's rationale and justification for the designation of compounds (b) (4) as the starting materials for GDC-0449?

**FDA Response:** Based on the information provided in the briefing document, FDA agrees that (b) (4) are acceptable starting materials. (b) (4) the level of impurity (b) (4) in the starting material (b) (4) and provide adequate control strategies, including purging studies, to limit the amount of the following impurities in the API:

(b) (4)

In addition, provide the acceptable 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 materials.

**Meeting Discussion:** Genentech acknowledged receipt of and agreed with FDA's preliminary responses. (b) (4)

FDA recommended that Genentech include sufficient scientific justification to support acceptance criteria in the NDA, including a thorough discussion of how the impurities are formed and how they are or are not carried through. Genentech agreed to provide sufficient scientific justification to demonstrate process understanding in the NDA,

**Question 2:** Based on the information provided on the development of the process proposed for commercial manufacturer, does the agency agree that Genentech's plans for the analytical assessment of future lots of API are appropriate to demonstrate that such lots will be of comparable quality to the lots used in the pivotal role?

**FDA Response:** Based on the information provided on the development of the process, your strategy appears reasonable to ensure the quality of the drug substance. Qualify any individual impurity above the qualification threshold level as per ICH Q3A. Adequacy will be determined at the time of NDA review.

**Meeting Discussion:** Participants accepted the topic as presented in the preliminary responses. No discussion occurred at the meeting.

**Question 3:** Does the Agency have any concerns with Genentech's proposed strategy for API process validation to support registration?

**FDA Response:** Process validation involves an objective, scientific demonstration of process control so that batches of active pharmaceutical ingredients (APIs) or drug product consistently meet documented specifications. Process validation is a CGMP requirement for finished pharmaceuticals under 21 CFR §211.100(a) and 21 CFR §211.110(a) and for APIs under the Food Drug and Cosmetic Act. This requirement must be met before product is commercially distributed and then maintained during commercialization. The status of process validation is periodically assessed to assure ongoing state of control. Processes must be capable, maintained as stable, and assured by robust monitoring methods to verify the process is in control.

We do not approve process validation protocols and plans. During on site inspections, FDA field staff will evaluate validation protocols and studies.

We support your efforts to gain process understanding and use experimental design to study critical process parameters and critical quality attributes. A good understanding of the variables, both material attributes and processing parameters, in each unit operation that impact the API's or drug product's specifications and quality attributes, will enable you to generate a sound protocol(s) for the commercial scale performance qualification. For example, your protocol(s) should address the process performance criteria against which you will judge the success of your process validation study(ies). Protocols should also address the data and measurements to be collected, sampling plans, comparisons to be made between individual commercial runs included in the study(ies), and the scientific data analyses, including any statistical analyses, to be performed on all the data collected. A scientific rationale for the protocol design should be available.

Although the FDA does not approve validation protocols, the Office of Compliance will meet to discuss your validation program questions in greater detail at a meeting scheduled for this purpose and may request participation by the appropriate FDA district office. Submit your request for such a meeting to the Office of Compliance following the Guidance for Industry, *Formal Meetings With Sponsors and Applicants for PDUFA Products*. As you develop your validation program, please consider FDA's draft revisions to the Guidance to Industry, *General Principles of Process Validation*, published in November 2008.

In addition, you should consider the development of a Quality by Design (QbD) approach to mitigate risk during the process and to allow process flexibility while ensuring quality.

**Meeting Discussion:** Genentech acknowledged receipt of FDA's preliminary responses. Genentech requested input on what a QbD application should contain. Quality by Design (QbD) concepts were discussed briefly. FDA referenced ICH Guidances Q8(R1), Q9, and Q10 and emphasized that a QbD approach demonstrates scientific understanding of process and possible multivariate interactions. In such an approach, risk analysis is also used to identify critical process parameters and to establish appropriate controls. Genentech stated that their validation program will be traditional with understanding of process, and they do not intend to include PAT. FDA emphasized that Genentech has the option to request a formal meeting with FDA to discuss their proposed QbD approach prior to NDA submission.

**Question 4:** Does the Agency agree that Genentech's proposed primary stability strategy is adequate to support registration?

**FDA Response:** The proposed primary stability strategy appears to be acceptable. Adequacy of the stability data will be determined at the time of NDA review.

**Meeting Discussion:** Participants accepted the topic as presented in the preliminary responses. No discussion occurred at the meeting.

**Question 5:** Does the Agency agree with Genentech's strategy and approach to setting the commercial specification for API?

**FDA Response:** The proposed strategy for setting the commercial specification is not adequate.

When reporting impurities in the drug substance, follow ICHQ3A(R2). Report organic impurities as individual specified identified impurities, individual specified unidentified impurities, individual unspecified impurities, and total impurities. Justify all specifications using scientific rationale and historical batch data.

In addition, include Residue on Ignition (USP<281>) as one of the critical attributes in Table 5.5.1-1.

Adequacy will be determined at the time of NDA review.

**Meeting Discussion:** Genentech acknowledged receipt of and agreed with FDA's preliminary responses. Genentech committed to ensure that the specifications and acceptance criteria are in accordance with ICH Q3B (R2) as well as for toxicology and safety. FDA acknowledged that Genentech included Residue on Ignition (USP<281>) as one of the critical attributes in Table 5.5.1-1.

## 2.2 DRUG PRODUCT

**Question 6:** Does the Agency have any concerns with Genentech's proposed strategy for Drug Product process validation to support registration?

**FDA Response:** See response to Question 3.

**Meeting Discussion:** Participants accepted the topic as presented in the preliminary responses. No discussion occurred at the meeting.

**Question 7:** Does the Agency agree that Genentech's proposed Drug Product primary stability strategy is adequate to support registration? In particular, does the Agency agree that the use of unprinted capsules in the primary stability program is acceptable to support stability claims for capsules bearing the final commercial image?

**FDA Response:** The stability strategy appears to be acceptable. Adequacy will be determined at the time of NDA review. The expiration dating period will be determined based on the data provided at the time of NDA filing.

Agency agrees that the use of unprinted capsules in the primary stability program is acceptable to support stability claims for capsules bearing the final commercial image.

**Meeting Discussion:** Participants accepted the topic as presented in the preliminary responses. No discussion occurred at the meeting.

**Question 8:** Does the Agency agree with Genentech's strategy and approach to setting the commercial specification for Drug Product?

**FDA Response:** Your overall strategy and approach to setting the commercial specification appear to be acceptable. Adequacy will be determined at the time of NDA review.

Agency recommends the use of one specification for release and stability of the Drug Product.

**Meeting Discussion:** Participants accepted the topic as presented in the preliminary responses. No discussion occurred at the meeting.

**Question 9: Does the Agency have any CMC concerns or recommendations for Genentech with respect to the anticipated GDC-0449 NDA filing?**

**FDA Response:** No further comments at this time. Adequacy of the CMC information will be determined at the time of NDA review.

**Meeting Discussion:** Participants accepted the topic as presented in the preliminary responses. No discussion occurred at the meeting.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

### **4.0 ACTION ITEMS**

There are no action items with specific due dates as a result of the meeting discussion. Recommendations to and commitments by the meeting participants are included in the meeting discussion section.

### **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**

The following pages include slides that were distributed by Genentech at the meeting but not presented to facilitate the discussion. They are appended to these minutes for completeness.



## **GDC-0449 (Hedgehog Pathway Inhibitor) Type C CMC Meeting**

**Genentech / FDA**

29 April 2009

### *Agenda*

- Development program overview
- CMC timeline to NDA
- GDC-0449 API
  - API overview
  - Manufacturing process
- GDC-0449 Drug Product
  - Formulation overview
  - Manufacturing process
- Pre-Meeting Package questions

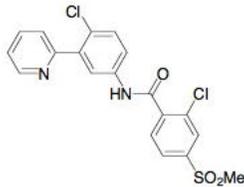


## Development Program Overview

- Proposed indication
  - GDC-0449 is indicated for the treatment of patients with advanced (metastatic or unresectable, locally advanced) basal cell carcinoma (BCC)
  - GDC-0449 has demonstrated encouraging anti-tumor activity with acceptable tolerability in patients with advanced BCC
  - There is a high unmet medical need, with no current standard of care
- Potential NDA filing in Q2-2011
  - Genentech would like End-of-Phase II level feedback on the CMC package in preparation for an NDA filing



## GDC-0449 API Overview



- Well characterized
  - Formation and control of impurities well understood
  - Manufacturing process consistently able to produce high-purity lots

(b) (4)

- Stable: long-term (>24 months) stability at 30°C/65% RH
- API specifications and stability programs will follow ICH guidelines

## GDC-0449 API Overview (cont'd)

- Manufacturing process

(b) (4)



## **GDC-0449 Drug Product Overview**

- Formulation
  - Standard capsule formulation with commonly used excipients
    - Commercial formulation locked prior to initiation of pivotal trial
    - No major changes planned
  - Stable product
    - No degradants have been observed during development
    - Long-term stability at 30°C/65% RH
      - Data will also be collected at 25°C/60% RH
- Manufacturing process

(b) (4)

## **GDC-0449 Drug Product Overview (cont'd)**

- DP specifications and stability programs will follow ICH guidelines
  - Discriminating in vitro dissolution method in place
- Running four or more lot campaigns to fully understand process capabilities
  - At commercial facility for the following:
    - NDA registration stability lots
    - Validation lots (at commercial scale)



## Pre-Meeting Package Questions

### API Questions

1. Does the Agency agree with Genentech's rationale and justification for the designation of compounds (b) (4) as the API starting materials for GDC-0449?
2. Based on information provided on the development of the process proposed for commercial API manufacture, does the Agency agree that Genentech's plans for the analytical assessment of future lots of API are appropriate to demonstrate that such lots will be of comparable quality to the lot used in the pivotal trial?
3. Does the Agency have any concerns with Genentech's proposed strategy for API process validation to support registration?
4. Does the Agency agree that Genentech's proposed API primary stability strategy is adequate to support registration?
5. Does the Agency agree with Genentech's strategy and approach to setting the commercial specification for API?

## Pre-Meeting Package Questions (cont'd)

### Drug Product Questions

1. Does the Agency have any concerns with Genentech's proposed strategy for Drug Product process validation to support registration?
2. Does the Agency agree that Genentech's proposed Drug Product primary stability strategy is adequate to support registration? In particular, does the Agency agree that the use of unprinted capsules in the primary stability program is acceptable to support stability claims for capsules bearing the final commercial image?
3. Does the Agency agree with Genentech's strategy and approach to setting the commercial specification for Drug Product?

### General Question

1. Does the Agency have any CMC concerns or recommendations for Genentech with respect to the anticipated GDC-0449 NDA filing?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-74573	GI-1	GENENTECH INC	GDC-0449 (SYSTEMIC HEDGEHOG PATHWAY ANTA
IND-74573	GI-1	GENENTECH INC	GDC-0449 (SYSTEMIC HEDGEHOG PATHWAY ANTA

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

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/s/

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DEBORAH M MESMER  
09/25/2009

Sarah Pope Miksinski  
09/28/2009



IND 74573

**SPECIAL PROTOCOL ASSESSMENT –  
NO AGREEMENT**

Genentech, Inc.  
Attention: Todd W. Rich, M.D.  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Rich:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0449 (Hedgehog pathway antagonist).

We also refer to your November 20, 2008 request, received on November 21, 2008, for a special protocol assessment of a clinical protocol. The protocol is titled “A Pivotal Phase II, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma”.

Special protocol assessment is designed to evaluate an individual protocol primarily in response to specific questions posed by the sponsor. Our assessment does not address your overall development strategy. Based on our review of your questions in the context of other submitted information, we have determined that the design and planned analysis of your study do not adequately address the objectives necessary to support a regulatory submission.

We have the following responses to your questions:

1. Does the Agency agree that this trial, if positive, along with supportive safety data from other Phase II randomized trials, would form the basis for a full approval for GDC-0449, for the treatment of patients with advanced BCC?

**FDA response (September 11, 2008): No.**

(b) (4)

2. Does the Agency agree that this trial, if positive for either metastatic or locally advanced BCC patients, along with supportive safety data from other Phase II randomized trials, would form the basis for a full approval for GDC-0449, for the treatment of patients with metastatic or locally advanced BCC, respectively?

**FDA response (September 11, 2008): No.** [REDACTED] (b) (4)

Company response to Questions 1 and 2 (November 20, 2008): Genentech asks the Agency to reconsider their No response for Questions 1 and 2 given that the Agency's specific issues have been addressed and their recommendations incorporated into the trial.

**FDA response (January 5, 2009): No.** [REDACTED] (b) (4)

3. Does the Agency agree that the metastatic and locally advanced BCC patient populations are appropriately defined?

**FDA response 3a (September 11, 2008): The proposed definition of metastatic BCC is acceptable.**

Company response (November 20, 2008): Genentech thanks the Agency for their response. The proposed definition for metastatic BCC in the revised protocol has not been changed from the protocol included in the previous SPA submission, reflecting the agreement between Genentech and the Agency.

**FDA response 3b (September 11, 2008): The proposed definition of locally advanced disease includes "patients with medical conditions predisposing to poor surgical outcome (e.g., diabetes with history of poor wound healing)." Patients who are too medically compromised to undergo surgical resection are generally not candidates for investigational therapy and therefore should not be enrolled on this study. In addition, patients with superficial multifocal basal cell carcinoma who may be considered unresectable due to breadth of involvement should be excluded because such patients can be treated with local therapy first.**

Company response (November 20, 2008): The following sentence has been deleted from the inclusion criteria, as reflected in Section 4.1.2 of the protocol (see Attachment A): [REDACTED] (b) (4)

[REDACTED] In addition, Genentech has added the following sentence to the exclusion criteria, as reflected in Section 4.1.3 of the protocol (see Attachment A): "*Patients with superficial multifocal BCC who may be considered unresectable due to breadth of involvement.*"

**FDA response (January 5, 2009): The proposed definition of the locally advanced BCC is acceptable with the following exception** [REDACTED] (b) (4)

**Since cutaneous lesions < 10 mm are inappropriate to be designated as target lesions, the FDA will consider patients with locally advanced BCC whose only target lesions were < 10 mm to have protocol violations and to be non-responders in the primary analysis.**

**Therefore, please revise this sentence to state “The externally visible component of all target lesions *must* be at least 10 mm in the longest dimension...”**

4. Does the Agency agree with the composite endpoint for locally advanced BCC, as defined in the protocol?

**FDA response 4 (September 11, 2008): No.**

Company response (November 20, 2008): Please see Company Responses to the Agency’s additional responses to Question 4 below.

**FDA response 4a (September 11, 2008): All measurable disease should be assessed in the evaluation of response, especially given the small size of the study.**

Company response (November 20, 2008): Genentech agrees (b) (4) (b) (4)

(b) (4) In addition, the size of the externally visible component of all target lesions has been increased (b) (4) to at least 10 mm, in order to assure that target lesions can be measured accurately and reproducibly (analogous to specifying the minimum size of target lesions that may be assessed by radiologic imaging per RECIST). This specification of minimum externally visible lesion size is intended to avoid the case where increase in the longest diameter of a BCC (b) (4) could be interpreted as progressive disease, when in fact the (b) (4) increase observed may be within the error of measurement.

**FDA response (January 5, 2009): These proposed changes are acceptable.**

**FDA response 4b (September 11, 2008): The table in Appendix C indicates that if the size component of a target lesion meets the criteria for SD and the ulcerative component meets the criteria for CR, the patient will be considered to have had a response. A change in tumor ulceration may reflect factors other than disease status (hygiene, local trauma, etc.). A change in tumor ulceration alone (i.e., without a size reduction) may not represent drug effect. This will need to be carefully documented with photographs. It will be important to demonstrate that your results are not driven by a patient subset with improvement only in tumor ulceration.**

Company Response (November 20, 2008): Genentech agrees. Changes in tumor ulceration will be carefully documented with photographs.

**FDA response (January 5, 2009): The issue that our response to 4b illustrates is broader than how tumor ulceration is documented. Patients with locally advanced disease whose clinical and RECIST components of their response may be discordant should be designated as having attained the lesser of the two responses. Please revise the table on page 4 of Appendix C accordingly.**

**FDA response 4c (September 11, 2008): Section C of Appendix C proposes that a new BCC lesion be considered as PD if it is >5 mm, is confirmed on biopsy to be BCC, and cannot be managed with standard therapy (e.g., surgical or topical). A new BCC should be considered PD irrespective of how it is managed.**

Company response (November 20, 2008): Genentech agrees. The reference to management by standard (e.g., surgical or topical palliation) has been removed, as reflected in Appendix C of the protocol (see Attachment A). A new BCC will be considered PD irrespective of how it is managed.

**FDA response (January 5, 2009): This is acceptable.**

**FDA response 4d (September 11, 2008): Although your question pertains to locally advanced disease, Section C of Appendix C also proposes that a new distant metastatic lesion must be confirmed on biopsy to be BCC to be considered PD. Any new lesion suspected of being BCC should be considered PD unless a biopsy conclusively proves otherwise. New lesions which are not biopsied or are histologically inconclusive should be considered PD.**

Company Response (November 20, 2008): Genentech agrees. The protocol has been revised to state that if a new lesion is not biopsied or the histology is inconclusive, it should be considered to be BCC and indicative of PD (see Section C of Appendix C of the protocol [Attachment A]).

**FDA response (January 5, 2009): Page 2 of the revised Appendix C contains the sentence,**

**Please remove this sentence, as it is inconsistent with your response above.**

**FDA response 4e (September 11, 2008): The final paragraph of Appendix C proposes that if all previously inoperable target lesions are rendered operable with clear margins obtained at surgery, this will be considered a CR. Patients who undergo resection of existing lesions should not be considered complete responders. They may be considered partial responders if all PR criteria were met preoperatively. An exploratory analysis considering these patients as having had CRs may be performed.**

Company Response (November 20, 2008): Genentech agrees. The final paragraph of Appendix C has been revised to state that if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR.

**FDA response (January 5, 2009): No.**

**FDA response 4f (September 11, 2008): Appendix G states, "If a baseline biopsy is found to be uninterpretable, no further biopsy will be requested." Patients with uninterpretable baseline biopsies should not have been initially eligible for the protocol. Any patient without an initial biopsy conclusively showing BCC should not be counted as a responder.**

Company Response (November 20, 2008): Genentech would like to clarify the timing and purpose of archival tissue submission (for all patients) and baseline biopsy (for patients with locally advanced disease). Archival tissue will be reviewed by the independent pathologist to determine whether the patient's diagnosis is consistent with BCC. The intent of the baseline biopsy in patients with locally advanced disease is to allow for the determination of complete versus partial response, consistent with Genentech's previous discussion with the FDA on 28 April 2008. The independent pathologist's interpretation of the archival tissue and the new biopsy will not be available until after the patient has already enrolled in the study. We agree that patients for whom the independent pathologist's interpretation of archival tissue or baseline biopsy is not consistent with BCC should not be included in the primary analysis; this is reflected in changes in the protocol (Section 4.8.3) and SAP (Section 3.3) (see Attachments A and B, respectively). However, if a patient has archival tissue submitted that is consistent with BCC but has an uninterpretable baseline biopsy of a locally advanced lesion, and this patient experiences a clinical or clinical/RECIST response that is confirmed by the IRF(s), this patient will still be considered to have a PR, consistent with the SAP (Section 3.3) (see Attachment B).

**FDA response (January 5, 2009): No. Any patient whose baseline biopsy is uninterpretable may be excluded from the analysis but should not be subsequently designated as a responder.**

**FDA response 4g (September 11, 2008): Appendix G states, "Patients experiencing a clinical response whose biopsies show no evidence of residual BCC will be considered to have a complete response; those experiencing a clinical response, but whose biopsies show evidence of residual BCC, will be considered to have a partial response." The statistical analysis plan states, "CRs in the locally advanced cohort that are not histologically confirmed either because of an indeterminate or ambiguous result or complete absence of an assessment will be considered PRs."**

**Findings on skin biopsy are subject to sampling error. Therefore, for a patient with locally advanced disease to be considered a complete responder there should be complete clinical resolution of all lesions *and* a negative biopsy at the time of response.**

Company response (November 20, 2008): Genentech agrees that there was an inconsistency between Appendix G of the protocol and the SAP. The SAP has been revised to accurately reflect the protocol (see Attachment B). Genentech understands that a patient with locally advanced disease to be considered a complete responder should have complete resolution of all lesions and a negative biopsy at the time of response, and the updated SAP and protocol are consistent with this.

**FDA response (January 5, 2009): This is acceptable.**

**FDA response 4h (September 11, 2008): Your response criteria propose that new ulceration not related to tissue biopsy or other known trauma and persisting for at least 2 weeks be**

**considered PD. Please clarify whether “not related to tissue biopsy” means that it is a separate location.**

Company response (November 20, 2008): Genentech agrees, and clarification is provided in Appendix C of the protocol that “not related to tissue biopsy” means that it is in a separate location (see Attachment A).

**FDA response (January 5, 2009): This is acceptable.**

5. Does the Agency agree with the guidelines for tissue biopsy in patients with locally advanced BCC?

**FDA response (September 11, 2008): The proposed technical procedures for tissue biopsy (timing, size of biopsy needle, etc.) appear acceptable.**

Company response (November 20, 2008): Genentech thanks the Agency for their response. The proposed technical procedures for tissue biopsy have not been changed from the protocol included in the previous SPA submission, reflecting the agreement between Genentech and the Agency.

**FDA response (January 5, 2009): This is acceptable.**

6. Does the Agency agree that the eligibility criteria for locally advanced BCC patients are clearly and accurately captured in the Sample CRF?

**FDA response (September 11, 2008): Yes.**

Company response (November 20, 2008): Genentech thanks the Agency for their response. The eligibility criteria for locally advanced BCC patients in the Sample CRF have not been changed from the protocol included in the previous SPA submission, other than as noted in the answers to FDA response 3b, reflecting the agreement between Genentech and the Agency.

**FDA response (January 5, 2009): This is acceptable.**

7. Does the Agency agree with our plan for review and confirmation of response, as outlined in the IRF charter for centralized reading of tumor scans and the IRF charter for the standardized digital photography of skin lesions?

**FDA response 7a (September 11, 2008): Protocol Section 4.4.1(e) indicates that radiographic responses (for all patients with metastatic disease and for those patients with locally advanced disease and a radiographically measurable component) will be determined by investigators and subsequently reviewed by an IRF. The FDA will consider any patient for whom an investigator stopped treatment because of suspected progression but whom the IRF subsequently considered stable as having progressed at the time treatment was discontinued. We therefore recommend that you use IRF readings to guide treatment decisions in real time if possible.**

Company response (November 20, 2008): Genentech thanks the Agency for their response and will take this under consideration.

**FDA response (January 5, 2009): We reiterate our earlier response. In patients where there are discrepancies between investigator and IRF-adjudicated progression dates, the FDA will consider progression to have occurred on the earlier of the two dates.**

**In addition, protocol Section 4.2.1 states, “If the investigator’s assessment of progressive disease is equivocal, and in the investigator’s opinion the patient is still deriving benefit from treatment, treatment with GDC-0449 should be continued, and the patient should be re-evaluated at the next tumor assessment time point.” It is not clear what you mean by an “equivocal” investigator’s assessment of progressive disease. The FDA will consider progression to have occurred at the time of either an “equivocal” assessment or when determined by the independent adjudicator (radiologist, photographer, or pathologist), whichever was first, irrespective of whether the investigator believes the patient is still benefiting from treatment.**

**FDA response 7b (September 11, 2008): Please specify who at [REDACTED] (b)(4) will interpret the digital photographs of target lesions (protocol Appendix H) and their training for expertise in this task. To account for interobserver variability, we strongly recommend that two reviewers interpret each photograph independently, and that a third interpreter do so in the event of discordance between the first two. Analogous to your Sequential Locked Review paradigm for reading radiographic studies, the reviewers should not communicate with one another about individual assessments.**

Company response (November 20, 2008): Genentech agrees. The reviewers will not be employees of [REDACTED] (b)(4) but will be independent investigators not associated with Genentech or with Study SHH4476g. We have specified the qualifications of the reviewers who will be contracted by [REDACTED] (b)(4) to interpret the digital photographs of target lesions and have specified the roles and procedures for the reviewers and adjudicator consistent with the FDA’s response, as reflected in the revised IRF Charter for the Standardized Digital Photography of Skin Lesions (see Attachment D).

**FDA response (January 5, 2009): Attachment D indicates that three board certified dermatologists and/or oncologists specializing in cutaneous tumors will interpret the digital photographs. This is acceptable.**

**FDA response 7c (September 11, 2008): Protocol Appendix G indicates that pathology slides reviewed by Genentech will also be sent to an independent pathologist. We strongly recommend that the two pathology readings be conducted independently. Analogous to your Sequential Locked Review paradigm for reading radiographic studies, the Genentech pathologist and independent pathologist should not communicate with one another about individual assessments. This should also apply to the third pathologist in the event of discordance between the Genentech pathologist and the independent pathologist.**

Company response (November 20, 2008): Genentech understands the Agency's concern. In order to minimize bias, the pathology slides will not be reviewed by Genentech. The pathology slides will now be read by an independent pathologist only, as reflected in Appendix G of the protocol (see Attachment A).

**FDA response (January 5, 2009): This is acceptable.**

8. Does the Agency agree with the Statistical Analysis Plan for the trial? Specifically, does the Agency agree with the separate assessment and analysis for the metastatic and locally advanced BCC patients (ORR significantly higher than 0.10 for metastatic BCC and significantly higher than 0.20 for locally advanced BCC)?

**FDA response (September 11, 2008): We agree with separate analyses for the metastatic and locally advanced cohorts. However, we do not believe that response rates of 10% for metastatic disease and 20% for locally advanced disease represent clinically meaningful benefit. The adequacy of the observed response rates to support approval in both metastatic and locally advanced disease will be a review issue. Time to event endpoints can only be considered as descriptive data in a non-randomized single arm study. You have not provided guidance on how to handle missing assessments in your primary analysis in your SAP.**

Company response (November 20, 2008): Genentech thanks the Agency for their response, and understands that the adequacy of the observed rates to support approval in both metastatic and locally advanced disease will be a review issue. Genentech has incorporated guidance on how to handle missing assessments in the primary analysis, as reflected in the SAP (see Attachment B, Section 3.7).

**FDA response (January 5, 2009): We reiterate our prior response. A registration trial that demonstrates response rates of 10% for metastatic disease and 20% for locally advanced disease may not be sufficient to support drug approval and will likely require ODAC discussion.**

**In addition, we strongly advise against imputing missing or uninterpretable data. Please provide the primary efficacy results based on all treated patients and all enrolled patients separately.**

9. Does the Agency agree with the sparse PK sampling in the proposed trial?

**FDA response (September 11, 2008): Yes, it appears generally acceptable.**

Company response (November 20, 2008): Genentech thanks the Agency for their response. The sparse PK sampling has not been changed from the protocol included in the previous SPA submission, reflecting the agreement between Genentech and the Agency.

**FDA response (January 5, 2009): This is acceptable.**

- 10. FDA comment 1: (September 11, 2008): Protocol Section 3.6 states that study drug treatment may be interrupted for up to 4 weeks for intolerable toxicity or up to 8 weeks for a planned surgical procedure. Patients with an asymptomatic or manageable severe adverse event may continue to receive study drug. If treatment is restarted after an interruption, no dose reduction will be allowed. For safety considerations, the dose modification guidelines should be revised as follows:**
- a. “Intolerable” toxicity should be defined *a priori*.**
  - b. Treatment that is restarted after a dose interruption should be at a reduced dose.**

Company response (November 20, 2008): Genentech agrees that “intolerable” toxicity should be defined *a priori*, and this is reflected in Section 3.6 of the protocol (see Attachment A). Genentech understands that the Agency requests that treatment that is restarted after a dose interruption should be at a reduced dose. Doses lower than 150 mg were not evaluated in the Phase I study because dose-related toxicities were not observed and encouraging evidence of clinical efficacy was observed at the 150-mg dose. In addition, animal studies were not predictive of human PK, and the dose dependence of the observed nonlinear absorption and/or clearance is not understood, precluding the prediction of an appropriate lower dose in humans. Therefore, only 150-mg capsules will be used in this Phase II study.

**FDA response (January 5, 2009): Patients who have two dose interruptions should either have a dose reduction or go off study.**

- 11. FDA comment 2 (September 11, 2008): The protocol does not prohibit any specific concomitant medications, but rather recommends that concomitant medications be used with care and provides a table of medications that may potentially interact with GDC-0449 (Appendix F). This table lists substrates, inducers and inhibitors of CYP2C8, CYP2C9, and CYP2C19. Given the *in vitro* P450 profiling of GDC-0449 (an inhibitor of CYP2C8, CYP2C9, and CYP2C19, but a substrate of CYP3A4), it would seem more appropriate to list *substrates* of CYP2C8, CYP2C9 and *inhibitors* of CYP3A4.**

Company response (November 20, 2008): Genentech agrees that because GDC-0449 is metabolized by CYP3A4 *in vitro* (albeit to a minimal extent), CYP3A4 inhibitors (and CYP3A4 inducers) should be used with caution when co-administered with GDC-0449. While not in tabular format, a list of CYP3A4 inhibitors and inducers that should be used with caution and documented in the CRFs is provided in the second paragraph of Appendix F of the protocol (see Attachment A). As suggested by the Agency, the table in Appendix F of the protocol lists CYP2C substrates, but not CYP2C inducers and inhibitors, with the potential to interact with GDC-0449.

**FDA response (January 5, 2009): This is acceptable.**

- 12. Protocol Section 5.2.3 provides guidelines for investigators to assign causality to adverse events. We do not recommend expressing causality as a simple “yes or no” response. We recommend that you consider a third category of possibly drug related.**

Company Response (November 20, 2008): Genentech wishes to clarify that the “yes” response includes the category of possibly drug related. Please refer to Table 2 of the protocol (see below), which indicates that if a causal relationship is possible, the investigator’s assessment with respect to drug relatedness should be “yes.” We understand that this is a more conservative approach than the approach suggested by the Agency.

**FDA response (January 5, 2009): This is acceptable.**

13. Genentech thanks the Agency for their responses and comments sent on 11 September 2008, and we have incorporated the Agency’s feedback. Does the Agency agree that the issues outlined in the Agency’s responses and comments in September have been adequately addressed in the new SPA request? Does the Agency agree to grant us a SPA agreement?

**FDA response (January 5, 2009): No.**

(b) (4)

Although we do not agree on the issues you posed, this does not preclude you from conducting this study under your IND. If you choose to submit a revised protocol for special protocol assessment (SPA) prior to study initiation, it should address all the issues itemized above and should be submitted as a new request for SPA.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products). This meeting would be limited to discussion of this protocol.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

*{See appended electronic signature page}*

Robert Justice, MD  
Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 74573

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GENENTECH INC

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GDC-0449 (SYSTEMIC HEDGEHOG  
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/s/  
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ROBERT L JUSTICE

01/05/2009



IND 74573

Genentech Inc.  
Attention: Todd W. Rich, M.D.  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Rich:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0449.

We acknowledge receipt of your July 31, 2008, request on August 1, 2008, for a special clinical protocol assessment. The protocol is titled A Pivotal Phase 2, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma.

We have completed our review and have determined that the design and planned analysis of your study do not adequately address the objectives necessary to support a regulatory submission. We have the following responses to your questions:

#### Questions

1. Does the Agency agree that this trial, if positive, along with supportive safety data from other Phase II randomized trials, would form the basis for a full approval for GDC-0449, for the treatment of patients with advanced BCC?

**FDA response:** No. [REDACTED] (b) (4)

2. Does the Agency agree that this trial, if positive for either metastatic or locally advanced BCC patients, along with supportive safety data from other Phase II randomized trials, would form the basis for a full approval for GDC-0449, for the treatment of patients with metastatic or locally advanced BCC, respectively?

**FDA response:** No. [REDACTED] (b) (4)

3. Does the Agency agree that the metastatic and locally advanced BCC patient populations are appropriately defined?

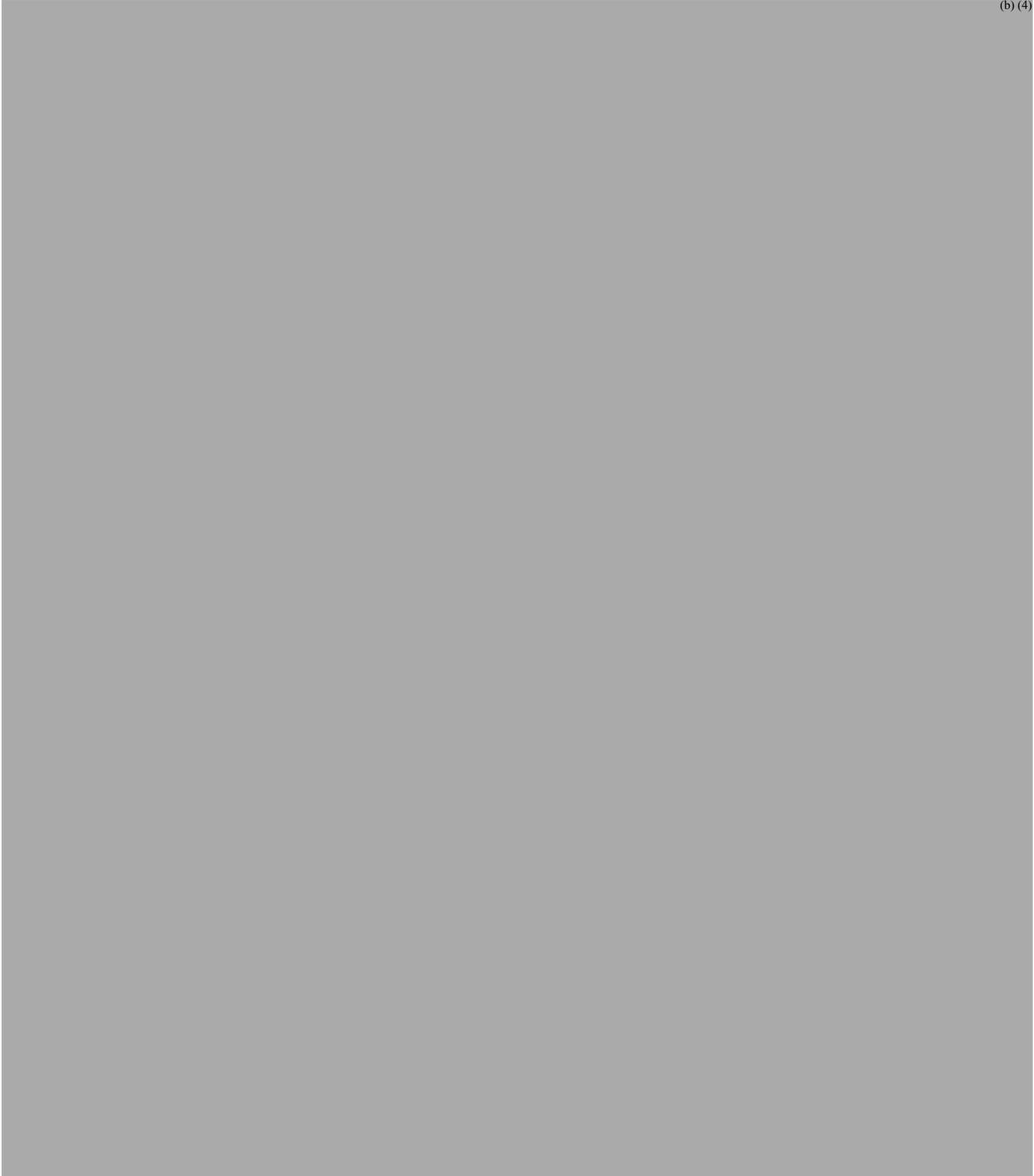
**FDA response:**

- a. The proposed definition of metastatic BCC is acceptable.
- b. The proposed definition of locally advanced disease includes “patients with medical conditions predisposing to poor surgical outcome (e.g. diabetes with history of poor wound healing).” Patients who are too medically compromised to undergo surgical resection are generally not candidates for investigational therapy and therefore should not be enrolled on this study.

**In addition, patients with superficial multifocal basal cell carcinoma who may be considered unresectable due to breadth of involvement should be excluded because such patients can be treated with local therapy first.**

4. Does the Agency agree with the (b) (4) for locally advanced BCC, as defined in the protocol?

**FDA response: No.**



5. Does the Agency agree with the guidelines for tissue biopsy in patients with locally advanced BCC?

**FDA response:** The proposed technical procedures for tissue biopsy (timing, size of biopsy needle, etc.) appear acceptable.

6. Does the Agency agree that the eligibility criteria for locally advanced BCC patients are clearly and accurately captured in the Sample CRF?

**FDA response:** Yes.

7. Does the Agency agree with our plan for review and confirmation of response, as outlined in the IRF charter for centralized reading of tumor scans and the IRF charter for the standardized digital photography of skin lesions?

**FDA response:**

- a. Protocol Section 4.4.1(e) indicates that radiographic responses (for all patients with metastatic disease and for those patients with locally advanced disease and a radiographically measurable component) will be determined by investigators and subsequently reviewed by an IRF. The FDA will consider any patient for whom an investigator stopped treatment because of suspected progression but whom the IRF subsequently considered stable as having progressed at the time treatment was discontinued. We therefore recommend that you use IRF readings to guide treatment decisions in real time if possible.
  - b. Please specify who at (b) (4) will interpret the digital photographs of target lesions (protocol Appendix H) and their training for expertise in this task. To account for interobserver variability, we strongly recommend that two reviewers interpret each photograph independently, and that a third interpreter do so in the event of discordance between the first two. Analogous to your Sequential Locked Review paradigm for reading radiographic studies, the reviewers should not communicate with one another about individual assessments.
  - c. Protocol Appendix G indicates that pathology slides reviewed by Genentech will also be sent to an independent pathologist. We strongly recommend that the two pathology readings be conducted independently. Analogous to your Sequential Locked Review paradigm for reading radiographic studies, the Genentech pathologist and independent pathologist should not communicate with one another about individual assessments. This should also apply to the third pathologist in the event of discordance between the Genentech pathologist and the independent pathologist.
8. Does the Agency agree with the Statistical Analysis Plan for the trial? Specifically, does the Agency agree with the separate assessment and analysis for the metastatic and locally advanced BCC patients (ORR significantly higher than 0.10 for metastatic BCC and significantly higher than 0.20 for locally advanced BCC)?

**FDA response:**

We agree with separate analyses for the metastatic and locally advanced cohorts. However, we do not believe that response rates of 10% for metastatic disease and 20% for locally advanced disease represent clinically meaningful benefit. The adequacy of the observed response rates to support approval in both metastatic and locally advanced disease will be a review issue.

Time to event endpoints can only be considered as descriptive data in a non-randomized single arm study.

**You have not provided guidance on how to handle the missing assessments in your primary analysis in your SAP.**

9. Does the Agency agree with the sparse PK sampling in the proposed trial?

**FDA response: Yes, it appears generally acceptable.**

**In addition, we have the following comments:**

- 1. Protocol Section 3.6 states that study drug treatment may be interrupted for up to 4 weeks for intolerable toxicity or up to 8 weeks for a planned surgical procedure. Patients with an asymptomatic or manageable severe adverse event may continue to receive study drug. If treatment is restarted after an interruption, no dose reduction will be allowed.**

**For safety considerations, the dose modification guidelines should be revised as follows:**

- a. “Intolerable” toxicity should be defined *a priori*.**
  - b. Treatment that is restarted after a dose interruption should be at a reduced dose.**
- 2. The protocol does not prohibit any specific concomitant medications, but rather recommends that concomitant medications be used with care and provides a table of medications that may potentially interact with GCD-0449 (Appendix F). This table lists substrates, inducers and inhibitors of CYP2C8, CYP2C9, and CYP2C19. Given the *in vitro* P450 profiling of GCD-0449 (an inhibitor of CYP2C8, CYP2C9, and CYP2C19, but a substrate of CYP3A4), it would seem more appropriate to list *substrates* of CYP2C8, CYP2C9, and CYP2C19 and *inhibitors* of CYP3A4.**
  - 3. Protocol Section 5.2.3 provides guidelines for investigators to assign causality to adverse events. We do not recommend expressing causality as a simple “yes or no” response. We recommend that you consider a third category of possibly drug related.**

If you wish to seek agreement with FDA via an SPA, you will need to submit a revised protocol that addresses all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the “*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*”). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Dillard Woody, Regulatory Project Manager, at (301) 796-4097.

Sincerely,

*{See appended electronic signature page}*

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

Linked Applications

Sponsor Name

Drug Name

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IND 74573

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GENENTECH INC

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GDC-0449 (SYSTEMIC HEDGEHOG  
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ROBERT L JUSTICE

09/11/2008

# MEETING/TELECON MINUTES

**MEETING DATE:** April 28, 2008

**TIME:** 12-1 PM      **LOCATION:** FDA/WO/Room 1309

**IND: Meeting Request Submission Date:** February 22, 2008

**Briefing Document Submission Date:** March 20, 2008

**DRUG:** GDC-0449 (Hedgehog pathway antagonist)

**SPONSOR/APPLICANT:** Genentech, Inc.

## **TYPE of MEETING:**

1. End-of-Phase 1, IND 74,573
2. Proposed Indication: Locally advanced or metastatic tumors

## **FDA PARTICIPANTS:**

### Division of Drug Oncology Products

Robert Justice, MD, Division Director-chair

Ramzi Dagher, MD, Division Deputy Director

Michal Brave, MD, Medical Reviewer

Susan Jenney, MS, Regulatory Project Manager

Dillard Woody, Regulatory Project Manager

Alice Kacuba, RN, MSN, RAC, Acting Chief, Project Management Staff

### Division of Dermatology and Dental Products

Patricia Brown, MD, Medical Reviewer

### Office of Clinical Pharmacology, Division of Clinical Pharmacology 5

Julie Bullock, PharmD, Acting Clinical Pharmacology Team Leader

Young Jin Moon, PhD, Clinical Pharmacology Reviewer

## **Office of Biostats (OB); Division of Biometrics 5 (DB 5)**

Rajeshwari Sridhara, PhD, Deputy Division Director, Division of Biometrics V (DB 5)

Xiaoping (Janet) Jiang, Ph.D., Math Statistician, DB 5

## **GENENTECH PARTICIPANTS:**

### Attendees in person:

Karen Jones, Director, Clinical Regulatory Affairs

Amita Joshi, Ph.D., Molecule Development Sub-team Leader (Director, Clinical Development PKPD)

Stuart Lutzker, M.D., Ph.D., Group Director, Head of Exploratory Clinical Development, BioOncology

Josina Reddy, M.D., Ph.D., Medical Director, Exploratory Clinical Development, BioOncology,  
Bao Truong, Regulatory Scientist, Clinical Regulatory Affairs  
Miki Yamamoto, Ph.D., Associate, Clinical Regulatory Affairs

(b) (4)

Attendees via phone :

Jennifer Decad, M.H.A., Manager, Clinical Regulatory Affairs  
Grazyna Lieberman, Ph.D., Associate Director, Clinical Biostatistics  
Jennifer Low, M.D., Ph.D., Medical Director, Exploratory Clinical Development, BioOncology,  
Howard Mackey, Ph.D., Senior Biostatistician, Clinical Biostatistics

**BACKGROUND:** The sponsor has requested this EOP1 meeting to receive feedback on whether the target population is appropriately defined for the proposed study in advanced BCC, to obtain feedback on whether the proposed tumor assessment endpoints represent an appropriate measure of clinical benefit for patients with advanced BCC, and to obtain feedback on whether the proposed study, in addition to supportive Phase II trials in metastatic colorectal and ovarian cancer, is adequate to characterize the safety and efficacy of GDC-0449 and hence sufficient to support approval of GDC-0449 in advanced BCC.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

Questions

1.
  - a. Does the Agency agree that the metastatic and unresectable, locally advanced BCC patient population appropriately defined?

**FDA: The metastatic BCC population is appropriately defined. However, the locally advanced population seems to be defined by general subjective criteria. Please provide more specific criteria for defining unresectability.**

**Tumors which are unresectable by Mohs surgery are generally those in which the tumor impinges upon vital structures such as major nerves and arteries. In most cases, especially in the head and neck area, invasion into muscle, fascia, and cartilage does not make a tumor unresectable. Madani<sup>1</sup> et al. studied incomplete Mohs surgery (MMS) and found that of 10,346 procedures 15 were identified as incomplete. Records were available in 14 cases. Tumors included 9 basal cell and 4 squamous cell carcinomas. “Of the unresectable cases, MMS was terminated because of ongoing multifocal positive skin margins, bony invasion, or extension of tumor to other locations.”**

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<sup>1</sup> Madani S, Huilgol SC, and Curruthers A. Unplanned incomplete MOHS micrographic surgery. J Am Academy of Dermatology. 2000 May;42(5 pt 1):814-9.

The surgical specialists specified by you includes “dermatologic surgeon” which is vague and could indicate almost any dermatologist. The Division would recommend that unresectability be determined by a Mohs micrographic surgeon or a head and neck surgeon. This recommendation is based on the fact that Mohs micrographic surgery is a specific technique for which surgeons receive specialized fellowship training.

An additional factor that should be incorporated into the definition of unresectability is the subtype of basal cell carcinoma being treated. Superficial multifocal basal cell carcinoma may be present at many points along a margin and be considered unresectable because of breadth of involvement; however, a patient with this type of basal cell carcinoma may be treated with local therapy first.

*Meeting Discussion: The sponsor will provide more detailed criteria for defining the locally advanced patient population. This may include patients for whom further surgery may be medically contraindicated or who are unresectable but may not receive radiation therapy or who previously received radiation therapy. The sponsor acknowledged that patients with superficial multifocal basal cell carcinoma should be excluded.*

- b. Does the Agency agree that advanced BCC, as defined, constitutes an appropriate unmet medical need?

**FDA: Please clarify the intent of your question. We agree that metastatic or truly unresectable BCC represents an unmet medical need. See response to Question 1a.**

*Meeting Discussion: The sponsor clarified that they will be requesting fast track designation.*

- c. Does the Agency agree that a pivotal Phase II/III study in advanced BCC should include both patients with RECIST-measurable and those with non-RECIST-measurable disease?

**FDA:** We do not believe it is possible to adequately evaluate the efficacy of the drug in both RECIST-measurable and non-RECIST-measurable disease in one analysis due to the differences in defining the patient populations and the proposed endpoints. You should assess and analyze the objective response rate separately for each of the two patient populations.

For patients with locally advanced disease, a primary endpoint based on assessment of cutaneous lesions may be acceptable if it is adjudicated by independent review of the digital photography information and if the patient population is more specifically defined. See also other considerations in the response to Question 2.

*Meeting Discussion: The sponsor agrees that the 2 populations should be assessed and analyzed separately.*

2.
  - a. Does the Agency agree that the composite endpoint, as defined, is appropriate to measure tumor responses in patients with non-RECIST-measurable advanced BCC and supports approval?

**FDA:** No.

1. Your proposed definition for complete response may be acceptable if it includes complete disappearance of the tumor confirmed by appropriate histologic confirmation and digital photography. The response endpoint could also include conversion from unresectable disease to resectable disease.
2. We have concerns about your proposed PR criteria given the subjectivity of the proposed elements.

*Meeting Discussion: The sponsor acknowledges that the CR definition may be acceptable and will consider the Division's comments on PR definition. One approach to refining the PR definition would be to consider complete flattening of nodular lesions and complete re-epithelialization of ulcerating lesions as PRs.*

- b. Does the Agency agree that overall response rate (inclusive of partial and complete responses per RECIST and composite tumor response criteria) is an appropriate endpoint for demonstrating clinical benefit in patients with advanced BCC and supports approval?

**FDA:** No, see above.

*Meeting Discussion: None*

- c. Would response rate significantly higher than 20% with a median duration of 6 months be considered clinically meaningful in advanced BCC?

**FDA:** Please see above.

*Meeting Discussion: None*

3. In consideration of the high unmet medical need and low prevalence of patients with advanced BCC, does the Agency agree that the proposed studying advanced BCC, does the Agency agree that the proposed study in advanced BCC and the additional supportive Phase II trials in metastatic colorectal and ovarian cancer would be adequate to characterize the safety and efficacy of GDC-0449 to support full approval for the treatment of patients with advanced BCC? (see Sections 7.1 and 8).

**FDA: No. See above comments regarding the design of the proposed BCC study. The additional phase 2 trials may provide additional supportive safety information.**

*Meeting Discussion: Depending on the results, the patient population, and the response criteria the proposed single arm study in combination with the additional safety information may support approval.*

**Additional Clinical Pharmacology Comments:**

1. We recommend that you add sparse PK sampling in your proposed trial to explore the exposure- response relationships of GDC-0449.
2. We remind you that an estimated  $[I]/K_i$  ratio greater than 0.1 is considered positive and in vivo evaluation of GDC-0449's inhibition potential with a sensitive substrate will be needed. Please see the Drug-Drug Interaction website and relevant guidance at <http://www.fda.gov/cder/drug/drugInteractions/default.htm>
3. As GDC-0449 is metabolized by CYP3A4 and 2C9, we recommend that you conduct drug-drug interaction studies with strong inhibitors/inducers of CYP3A4 and 2C9.
4. We recommend that you conduct *in vitro* screens to determine if GDC-0449 is an inducer of CYP450. In addition an *in vitro* study to determine if GDC-0449 is a P-glycoprotein substrate or inhibitor should be conducted. Please refer to <http://www.fda.gov/cder/guidance/6695dft.pdf> for more information.
5. A formal food effect study needs to be conducted per the FDA guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies". This study should be conducted with your final-market-image formulation.
6. Address the absorption, distribution, metabolism and excretion (ADME study) of GDC-0449 in humans and if needed characterize the effect of renal and or hepatic impairment on the PK of GDC-0449.

7. **Do you have plans to develop an IV formulation or investigate different dosing schedules for oral administration given the long half life, saturable absorption and failure to reach the MTD.**
8. **According to 21 CFR 320.25, the bioavailability (absolute or relative) of GDC-0449 should be assessed.**

**ACTION ITEMS:** (Include description, identify person responsible and due date.)

1. None

Alice Kacuba  
Project Manager

Bob Justice  
Concurrence Chair

Linked Applications

Sponsor Name

Drug Name

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IND 74573

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GENENTECH INC

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GDC-0449 (SYSTEMIC HEDGEHOG  
PATHWAY ANTA

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/s/  
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ALICE KACUBA  
07/06/2008