

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761034Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
BLA # 761034	BLA Supplement # N/A	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Tecentriq® Established/Proper Name: atezolizumab Dosage Form: Liquid Single-Use Vial		Applicant: Genentech, Inc. Agent for Applicant (if applicable): Jerald Grace, PharmD; Regulatory Program Management
RPM: Kim J. Robertson		Division: DOP 1
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>September 12, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain <u>N/A</u>		<input checked="" type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

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

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

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

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

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

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

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

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

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) May 18, 2016
<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 <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included January 12, 2016
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included January 12, 2016
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included April 20, 2016
❖ 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> </ul>	June 20, 2015 June 17, 2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None March 11, 2016 DMEPA: <input checked="" type="checkbox"/> None March 22, 2016; April 27, 2016 DMPP/PLT (DRISK): April 19, 2016; April 21, 2016 (DRISK) <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> None April 20, 2016 SEALD: <input type="checkbox"/> None N/A CSS: <input type="checkbox"/> None N/a Product Quality <input checked="" type="checkbox"/> None May 3, 2016 Other: <input type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) March 11, 2016
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Included
❖ 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>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<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
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>March 2, 2016</u> If PeRC review not necessary, explain: <u>N/A</u></li> </ul>	
❖ Breakthrough Therapy Designation	<input type="checkbox"/>
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	Granted; May 22, 2014
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	May 22, 2014
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	February 3, 12, 16, 22, and 29 2016; March 4, 8, 9, 10, 11, 15, 17, 21(2), 24(2), 25, and 31, 2016; April 1, 5(2), 6, 8, 12, 13(2), 14, 20(7), 21(3), and 26(2), 2016; May 4(2), 12, and 17, 2016.
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	April 21, 2016
❖ Minutes of Meetings	
<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    May 11, 2015; September 24, 2015
<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>• <b>Mid-cycle</b> Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A    March 23, 2016
<ul style="list-style-type: none"> <li>• <b>Late-cycle</b> Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A    April 25, 2016
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	N/A
❖ 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>	N/A
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    May 18, 2016
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    May 17, 2016
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    May 3, 2016
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None    6
<b>Clinical</b>	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review Same as CDTL Review, May 3, 2016
• Clinical review(s) (indicate date for each review)		May 2, 2016
• Social scientist review(s) (if OTC drug) (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)		See Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)		<input checked="" type="checkbox"/> None QT-IRT; March 22, 2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)		<input checked="" type="checkbox"/> N/A
❖ Risk Management		
• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))		N/A
• REMS Memo(s) and letter(s) (indicate date(s))		N//a
• 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)		<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)		<input type="checkbox"/> None requested March 31, 2016
<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
<b>Biostatistics</b>		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review Combined with Clinical Review, May 3, 2016
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None Combined with Clinical Review, May 3, 2016
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None April 20, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None requested

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review April 27, 2016
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review April 26, 2016
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 21, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 13, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See Product Quality Review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> ) N/A
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done N/A
❖ <b>For Breakthrough Therapy (BT) Designated drugs:</b> • Notify the CDER BT Program Manager	<input checked="" type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> • Notify the Division of Online Communications, Office of Communications	<input type="checkbox"/> Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

NDA/BLA#: BLA# 761034 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: DOP 1 PDUFA Goal Date: 9/12/16 Stamp Date: 1/12/2016

Proprietary Name: Tecentriq

Established/Generic Name: atezolizumab

Dosage Form: Liquid Single-Use Vial, 1200 mg/20mL (60 mg/mL)

Applicant/Sponsor: Genentech, Inc.

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

- (1) N/A  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_
- 

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

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Metastatic Urothelial Bladder Cancer

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

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

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

- Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

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

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

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

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

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

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

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

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

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

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

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

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

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

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

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

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

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

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

**#** Not feasible:

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

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric

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

patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

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

Δ Formulation failed:

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

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*If there are additional indications, please complete the attachment for each one of those indications.*

*Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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

(Revised: 6/2008)

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

**Attachment A**

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

**Indication #2:** \_\_\_\_\_**Q1:** Does this indication have orphan designation?

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

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

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

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

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

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

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

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

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

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

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

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

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

# Not feasible:

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

\* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

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

(Revised: 6/2008)

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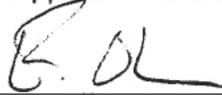
/s/  
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KIM J ROBERTSON  
02/19/2016

**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 atezolizumab in connection with this Biologic License Application at Genentech, Inc.

Signed by:



Eric Olson  
Vice President, Regulatory Affairs

10/6/2015

Date

## Robertson, Kim

---

**From:** Jerald Grace <grace.jerald@gene.com>  
**Sent:** Friday, May 13, 2016 2:16 PM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq

Ok thanks for this clarification.

On Fri, May 13, 2016 at 10:49 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

SRT (Safety Review Team).....they are currently reviewing the PMRs/PMCs, relative to FDAAA matters. SWAT is a part of them, but forgive me for not knowing what their acronyms stand for at the moment.

K

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:(301)796-1441)*

*Fax: [\(301\) 796-9845](tel:(301)796-9845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [mailto:[grace.jerald@gene.com](mailto:grace.jerald@gene.com)]  
**Sent:** Friday, May 13, 2016 1:28 PM

**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq

Youre Welcome.

Also--what was the name of that group that you mentioned was reviewing the Label, PMRs and PMCs? I think you mentioned it was SRT or SWAT?

On Fri, May 13, 2016 at 10:22 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Thank you for the confirmation Jerald.

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:(301)796-1441)*

*Fax: [\(301\) 796-9845](tel:(301)796-9845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [mailto:[grace.jerald@gene.com](mailto:grace.jerald@gene.com)]

**Sent:** Friday, May 13, 2016 1:01 PM

**To:** Robertson, Kim

**Subject:** Re: BLA 761034; Tecentriq

Hi Kim,

Yes I can confirm

(b) (4)

Jerald

On Fri, May 13, 2016 at 9:31 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hi Jerald:

I recall about a week ago, GNE was considering

(b) (4)

Can you confirm for me

(b) (4)

Thanks,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:(301)796-1441)*

*Fax: [\(301\) 796-9845](tel:(301)796-9845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
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(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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/s/  
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KIM J ROBERTSON  
05/17/2016

**Robertson, Kim**

---

**From:** Robertson, Kim  
**Sent:** Thursday, May 12, 2016 7:32 PM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA 761034; Tecentriq---Carton & Container Question

Excellent!! Thank you so much Jerald.  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Thursday, May 12, 2016 6:54 PM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq---Carton & Container Question

Hi Kim,

Yes this is correct--the version submitted on April 20th was the final version.

Regards,  
Jerald

On Thu, May 12, 2016 at 3:42 PM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hi Jerald:

Would you please confirm for me that GNE's submission dated April 20, 2016 contains the final version of the C&C labeling for Tecentriq?

Thanks,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:(301)796-1441)*

*Fax: [\(301\) 796-9845](tel:(301)796-9845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 |  (b) (6) |  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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/s/  
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KIM J ROBERTSON  
05/12/2016

**Balcazar, Pamela**

---

**From:** Balcazar, Pamela  
**Sent:** Friday, May 06, 2016 1:42 PM  
**To:** 'grace.jerald@gene.com'  
**Cc:** Robertson, Kim  
**Subject:** BLA 761034; Tecentriq (atezolizumab)

Good Afternoon

On behalf of my colleague Kim Robertson who is out of the office today, I have the following comment from our review team for BLA 761034 USPI.

*In the section on Ocular Inflammatory Toxicity that you have added to the Highlights, we recommend that you remove the phrase “(b) (4)”. We realize you are referring to grade 4 toxicity, but here grade 4 is blindness rather than (b) (4).*

*In terms of including toxicities covered under Warning 5.5 Other Immune-Related Adverse Reactions as individual Warnings in the Highlights, this is acceptable, (b) (4)*

If you have any questions, please let me or Kim know.

Regards,

*Pamela Balcazar, MS*

Regulatory Health Project Manager  
Food and Drug Administration (FDA)  
Office of Hematology and Oncology Products – DOP1  
10903 New Hampshire Ave.  
White Oak Bldg 22, Room 2133  
Silver Spring, MD 20993  
(240) 402-4203 (office)  
(301) 796-9845 (fax)  
[pamela.balcazar@fda.hhs.gov](mailto:pamela.balcazar@fda.hhs.gov)

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/s/  
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PAMELA I BALCAZAR  
05/06/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Wednesday, May 04, 2016 2:47 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Clinical Information Request

**Importance:** High

Hello again Jerald:

Please note that I am still awaiting word from Dr. Maher, relative to when I can send GNE the Tecentriq USPI with FDA remarks, but in the interim, please see the following request for information from the clinical discipline:

### **CLINICAL INFORMATION REQUEST:**

1. Provide the additional narrative details below:
  - a. Patient 101211 (PCD4989G) – Provide additional details regarding the event of “Arthritis infective” including clinical scenario, surgeries, results of joint fluid analysis, cultures, serum laboratories, and outcome.
  - b. Patient 102124 (PCD4989G) – Provide additional details regarding the event of “Arthritis infective” including clinical scenario, surgeries, results of joint fluid analysis, cultures, serum laboratories. Additionally, provide details regarding the event of “Device-related infection.”
  - c. Patient 101229 (PCD4989G) – Provide additional details regarding the event of “Meningitis” including clinical scenario, CNS imaging, results of CSF analysis, cultures, serum laboratories, and outcome.
  - d. Patient 101716 (PCD4989G) – Provide additional details regarding the event of “actiniomycosis” including clinical scenario, infected tissue(s) and outcome.
  - e. Patient 101716 (PCD4989G) – Provide additional details regarding the event of “fungal infection” including clinical scenario, infected tissue(s), cultures, and outcome.
  - f. Patient 181002 (G028625) – Provide additional details regarding the event of “coccidioidomycosis” including clinical scenario, infected tissue(s), cultures, serum laboratories, and outcome.
  - g. Patient 184002 (G028625) – Provide additional details regarding the event of “Disseminated herpes zoster infection” including clinical scenario, history of prior vaccination, cultures, HSV PCR, serum laboratories, and outcome.
  - h. Patient 203007 (G028753) – Provide additional details regarding the event of “osteomyelitis” including clinical scenario, location of affected bone and whether

this was related to patient's history of jaw necrosis, surgeries, cultures, , serum laboratories, and outcome.

- i. Patient 313047 (G028754) – Provide additional details regarding the event of “encephalitis” including clinical scenario, CNS imaging, results of CSF analysis, cultures, serum laboratories, and outcome.
- j. Patient 5002 (G029293) - Provide additional details regarding the event of “spinal cord infection” including clinical scenario, CNS imaging, results of CSF analysis, cultures, serum laboratories, and outcome.
- k. Patient 1141 (G029293) - Provide additional details regarding the non-encapsulated yeast forms seen on CSF analysis including whether this was considered by the Investigator to be related to the patient's encephalopathy, whether the patient received treatment for the yeast, and any further speciation and/or culture results.

For all patients, provide lymphocyte count at the time of infection (or the most proximate count to the onset of infection).

2. Provide the results of patients treated with atezolizumab across all clinical trials experience regarding incidence of the following infections:
  - a. Pneumocystis jirovecii (carinii) pneumonia
  - b. Candidiasis
  - c. Toxoplasmosis
  - d. Cryptococcosis
  - e. Cryptosporidiosis
  - f. Histoplasmosis
  - g. Isosporiasis

Please provide this information to us by **Tuesday, May 10, 2016, 3pm, EST.**

Thank you,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
05/04/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Wednesday, May 04, 2016 5:12 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--USPI with FDA Revisions/Edits  
**Attachments:** 04May16 atezolizumab USPI with FDA Revisions.doc

**Importance:** High

Hello Jerald:

Please see the attached Word .doc, as it is the Tecentriq™ (atezolizumab) USPI with FDA Revisions/Comments. Please review and provide us with either Genentech's concurrence, or any additional comments Genentech may have relative to our edits by **Tuesday, May 10, 2016, 3pm EST.**

Our comments/revisions can be found in Sections 2 and 5 of the label.

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
05/04/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Monday, April 25, 2016 8:51 AM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)---Additional PMR

**Importance:** High

Hello Jerald:

Relative to Genentech's BLA for Tecentriq (atezolizumab), clinical has an additional PMR:

### **PMR:**

### **Clinical:**

Conduct "G029294: A Phase III, Open-label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared with Chemotherapy in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer After Failure with Platinum-containing Chemotherapy" and provide a study report, datasets, and, if appropriate, revised labeling.

We need the following milestones for G029294:

Final Protocol Submission Date: September 12, 2014

Study/Clinical Trial Completion Date:

Final Study Report Submission Date:

Please provide a response to this PMR by **Wednesday, April 27, 2016, 2pm, EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
04/26/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Monday, April 25, 2016 8:58 AM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)---LCM Time Delay...  
**Importance:** High

Hello again Jerald:

Please note that the Agency is not going to be able to come on the line for our LCM today, until aprox. 3:10-3:15 pm EST, as there is now a need to hold internal discussions, prior to the meeting. If needed, this time will be added to the end of the hour. We ask that GNE still avails itself to us for 12pm PST, as we may be able to come on the line earlier.

Thank you,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/26/2016

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** April 14, 2016

**Application Number:** BLA #761034

**Product Name:** Tecentriq® (atezolizumab)

**Sponsor/Applicant Name:** Genentech, Inc.

**Subject:** Missing Adverse Events from Datasets

**FDA Participants :** Geoffrey Kim, MD, DOP1; Amna Ibrahim, MD, DOP1; Daniel Suzman, MD, DOP1; Yang-Min (Max) Ning, MD, PhD, DOP1; Jenn Sellers, PhD; OSI; Kim J. Robertson, DOP1

**Genentech, Inc. Participants :** Ben Lyons, PhD, Global Biometrics Team Lead; Melinda Teng, PhD, Sr. Statistical Scientist, Biostatistics; Shi Li, PhD, Statistical Scientist, Biostatistics; Kathie Winson, MS, Group Director, Product Development Regulatory (PDR); Daejin Abidoye, MD, Clinical Scientist, Pharma Development Oncology, Clinical Development; AnneChristine Thastrom, MS, PhD, Clinical Scientist, Pharma Development Oncology, Clinical Development; Jerald Grace, PharmD, Associate Regulatory Program Director, (PDR); Flavia DiNucci, MD, Safety Science Lead, Safety Science

**1.0 BACKGROUND:** During the inspection of Memorial Sloan-Kettering Cancer Center (MSKCC), it was noted that adverse events (AEs) that were entered in the eCRFs, were not included in the datasets. This involved 3 of 30 patients enrolled on the Phase 2 trial at that site. These AEs occurred well before the data cutoff of May 5, 2015. The following AEs were not included in the datasets:

Subject 1236: Cholecystitis [4/2/15-4/6/15 ] Grade 3 (SAE). Treatment interrupted.  
LFT abnormalities and sepsis were reported, but cholecystitis was not reported.

Subject 1074: Right Shoulder Pain: [12/1/14- ongoing] Grade 1  
Chills: [10/2/14- 9/29/15] Grade 1

Subject 1202: UTI: [10/15/14-10/27/15] Grade 2  
Back Pain: [10/7/14- 10/27/14] Grade 2  
Headache: [10/21/14- no end] Grade 1  
Weakness: [10/21/14- no end] Grade 1  
Rash: [10/27/14- during infusion] Grade 2  
Weakness: [12/3/14- not resolved] Grade 1  
elevated AST: [12/9/14-12/16/14] Grade 3  
elevated ALT: [12/9/14-12/16/14] Grade 2

**2.0 DISCUSSION:** The applicant stated that the AE discrepancies did not occur, due to transfer to the datasets, but it was a due to late entry by the site. It was stated that the MSKCC site had a Genentech generated audit that was performed on May 20, 2015; after the clinical cut-off of May 5, 2015. The audit found that these adverse events were omitted from the dataset. The Applicant did not state why the omission of these adverse events were not found and corrected by monitoring. The Applicant team at this teleconference stated that they were unaware of the audit findings and of the adverse events that were not included in the datasets until contacted by the FDA. Genentech stating that they were taking a systemic approach to see how widespread this issue is and that this is currently ongoing.

**3.0 ACTION ITEMS:** The Agency asked Genentech to provide the following:

- A timeline for submission of a report by April 15, 2016; This report will examine whether adverse events have been omitted from the datasets at other sites.
- Audit reports, corrective action plan(s) for any non-compliant sites, and how many sites required corrective actions during monitoring
- Tecentriq® (atezolizumab) USPI by April 15, 2016, excluding Sections 5 and 6

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/s/  
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KIM J ROBERTSON  
04/21/2016

VIRGINIA E MAHER  
04/21/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Thursday, April 21, 2016 5:58 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA #761034 Tecentriq (atezolizumab) USPI with Additional FDA Comments  
**Attachments:** 21April16 Proposed Tecentriq (atezolizumab) USPI-complementary with FDA Comments.docx

**Importance:** High

Hello again Jerald:

The attached MS Word .doc is the Tecentriq (atezolizumab) USPI with additional remarks/comments, inclusive of the comments DOP1 made 20April2016. Please review the label in its entirety, as these remarks were made in both the FPI and the MG.

Please review and return a full label to us, with any comments Genentech, Inc. may have, by **Tuesday, April 26, 2016 1pm, EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/21/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Thursday, April 21, 2016 5:14 PM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA 761034; Tecentriq--Late Cycle Meeting???  
**Attachments:** Final Late-Cycle Meeting Background Package BLA 761034 Tecentriq (atezolizumab) (COR-MEET-07).pdf

**Importance:** High

Hi Jerald:

Please see the attached .pdf document, as it is the Agency's Late Cycle Meeting (LCM) Background Package for the April 25, 2016 LCM meeting with Genentech, Inc..

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Thursday, April 21, 2016 10:22 AM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq--Late Cycle Meeting???

Thanks Kim,

Yes a T-con would be our preference as well.

We wanted to use the time to discuss a few items on the label and PMR/PMCs we received yesterday. Additionally as we are planning to submit the AE assessment tomorrow, we thought Monday's T-con would be a good opportunity to touch base with the Agency to see if there were any additional questions.

Jerald

On Thu, Apr 21, 2016 at 7:04 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

I will notify my team of this Jerald. Is there anything that Genentech would like to discuss in particular for this meeting? And may we presume this meeting is going to be a t-con?

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [mailto:[grace.jerald@gene.com](mailto:grace.jerald@gene.com)]

**Sent:** Wednesday, April 20, 2016 8:36 PM

**To:** Robertson, Kim

**Subject:** Re: BLA 761034; Tecentriq--Late Cycle Meeting???

Hi Kim,

I was actually in the process of drafting you a separate email on this exact topic :-)

After discussing with the team, we would like to keep the Late-Cycle meeting planned for Monday afternoon. Can we keep the 3-4:30 pm EST time frame as originally planned?

Jerald

On Wed, Apr 20, 2016 at 5:17 PM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hi Jerald:

Have you had an opportunity to discuss with your colleagues whether or not they would like to proceed with the Late Cycle Meeting slated for Monday, April 25, 2016? Aside from the requests for additional information that were conveyed today, it would seem that the only outstanding information of concern to the Division would be the relevant information pertinent to the late-entry AE reporting the Agency is waiting on that is due to us this Friday.

Please confirm.

Regards,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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KIM J ROBERTSON  
04/21/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Wednesday, April 20, 2016 8:18 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq--Late Cycle Meeting???

**Importance:** High

Hi Jerald:

Have you had an opportunity to discuss with your colleagues whether or not they would like to proceed with the Late Cycle Meeting slated for Monday, April 25, 2016? Aside from the requests for additional information that were conveyed today, it would seem that the only outstanding information of concern to the Division would be the relevant information pertinent to the late-entry AE reporting the Agency is waiting on that is due to us this Friday.

Please confirm.

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/20/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Tuesday, April 19, 2016 3:41 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab) --Clinical Information Request

**Importance:** High

Hello again Jerald:

Relative to Genentech's BLA for Tecentriq, the clinical reviewer has the following request for information:

### **CLINICAL INFORMATION REQUEST:**

In your report about the absence of some AEs from the datasets, Genentech will need to send the complete audit report. Please explain why Genentech was unaware of the audit report. Please be aware that we may have more questions after reading the report and that Genentech should attempt to answer the "spirit" of our concern in the report, rather than focus narrowly on specific questions.

Please also tell us.... what are CAPAs?

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/20/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Monday, April 18, 2016 6:54 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq--Proposed PMC & Milestone Information Request

**Importance:** High

Hello Jerald:

Relative to BLA 761034; Tecentriq, the clinicians are proposing the following Post Marketing Commitment (PMC):

- The submission of data concerning the overall survival and median duration of response for IMvigor 210 for the entire population and for each PD-L1 subset.

Final protocol was submitted:

Report submission:

---

Please also provide us with the following:

Milestones for study (b) (4)

Final Protocol Submission Date:

Study/Clinical Trial Completion Date:

Final Report Submission Date:

Please provide us with this information by **Tuesday, April 19, 2016; 12:30pm, EST.**

Regards,

Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/20/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Wednesday, April 20, 2016 7:06 PM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA #761034; Tecentriq (atezolizumab)--Clinical Information Request

Thank you Jerald.

I am preparing the PMRs/PMCs now to send them to Genentech.

Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Wednesday, April 20, 2016 6:46 PM  
**To:** Robertson, Kim  
**Subject:** Re: BLA #761034; Tecentriq (atezolizumab)--Clinical Information Request

Hi Kim,

Acknowledging receipt. Will send to team.

Also--any updates on when we can expect the updated label and PMRs/PMCs?

Jerald

On Wed, Apr 20, 2016 at 3:27 PM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hello Jerald:

Relative to Genentech's BLA for Tecentriq (atezolizumab), the clinical reviewer has the following request for information:

### **CLINICAL INFORMATION:**

Please provide additional detail regarding the case of herpetic meningoencephalitis that occurred in patient 1283, including results of imaging and CSF studies (including serologies and titers if performed), and the outcome of the case. A case of immune-related meningoencephalitis is mentioned in section 5.5 of the USPI – if this did not occur in patient 1283, provide additional details regarding this case.

Please provide a response to address this query by **Friday, April 22, 2016, 3:00pm EST.**

Regards,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:(301)796-1441)*

*Fax: [\(301\) 796-9845](tel:(301)796-9845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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KIM J ROBERTSON  
04/20/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Monday, April 18, 2016 11:46 AM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** April 14th T-Con---GNE Participants

Hi Jerald:

Would you please provide me with the names of the Genentech t-con attendees during last week's April 14<sup>th</sup> t-con? To reiterate, the following people attended from the FDA:

Geoffrey Kim, MD, DOP1; Amna Ibrahim, MD, DOP1; Daniel Suzman, MD, DOP1; Yang-Min (Max) Ning, MD, PhD, DOP1;  
Jenn Sellers, PhD, OSI; Kim J. Robertson, DOP1.

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/20/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Wednesday, April 20, 2016 7:06 PM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA #761034; Tecentriq (atezolizumab)--Clinical Information Request

Thank you Jerald.

I am preparing the PMRs/PMCs now to send them to Genentech.

Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Wednesday, April 20, 2016 6:46 PM  
**To:** Robertson, Kim  
**Subject:** Re: BLA #761034; Tecentriq (atezolizumab)--Clinical Information Request

Hi Kim,

Acknowledging receipt. Will send to team.

Also--any updates on when we can expect the updated label and PMRs/PMCs?

Jerald

On Wed, Apr 20, 2016 at 3:27 PM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hello Jerald:

Relative to Genentech's BLA for Tecentriq (atezolizumab), the clinical reviewer has the following request for information:

### **CLINICAL INFORMATION:**

Please provide additional detail regarding the case of herpetic meningoencephalitis that occurred in patient 1283, including results of imaging and CSF studies (including serologies and titers if performed), and the outcome of the case. A case of immune-related meningoencephalitis is mentioned in section 5.5 of the USPI – if this did not occur in patient 1283, provide additional details regarding this case.

Please provide a response to address this query by **Friday, April 22, 2016, 3:00pm EST.**

Regards,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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KIM J ROBERTSON  
04/20/2016

**Robertson, Kim**

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**From:** Robertson, Kim  
**Sent:** Wednesday, April 20, 2016 7:13 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq USPI with FDA Comments  
**Attachments:** 20April16 Proposed Tecentriq (atezolizumab) USPI-complementary with FDA Comments.docx

**Importance:** High

Hello Jerald:

Please see the attached MS Word .doc, as it is the Tecentriq (atezolizumab) USPI with DOP 1 comments. Please review and provide us with a return label by **Friday, April 22, 2016; 2:00pm EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/20/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Wednesday, April 20, 2016 7:34 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq --PMRs/PMCs  
**Attachments:** PMRs and PMCs for BLA 761034 Tecentriq (atezolizumab).doc

**Importance:** High

Hi Jerald:

The attached MS Word .doc contains the PMRs/PMCs, relative to Genentech's BLA for Tecentriq (atezolizumab). It is my understanding that Andrew Shiber may have already conveyed CMC's PMR/PMC to Genentech, but I thought I would send them with the other PMRs/PMCs.

\*Please note—the clinical proposed PMC's verbiage conveyed to Genentech on April 18<sup>th</sup>, has been *slightly* modified.

Please provide us with the milestone dates by **Friday, April 22, 2016; 2:00pm EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**PMRs and PMCs**  
**For**  
**BLA 761034; TECENTRIQ (atezolizumab)**

**PMRs:**

**CLINICAL:**

- Conduct a clinical trial to evaluate the effect of atezolizumab on thyroid function tests and clinical thyroid disease. Submit the completed report, datasets, and revised labeling.

Final protocol Submission Date:

Study/Clinical Trial Completion Date:

Final Report Submission Date:

Other:

**CMC:**

- Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that are expected to be present in samples at the time of patient sampling.

Final protocol Submission Date:

Study/Clinical Trial Completion Date:

Final Report Submission Date:

Other:

## **PMCs:**

### **CLINICAL:**

- Submit the median duration of response for all patients, all PD-L1 positive patients (IC 2/3), and all PD-L1 negative patients (IC 0/1) who responded to atezolizumab on IMvigor 210. Submit datasets and revised labeling concerning the median duration of response.

Final protocol Submission Date:

Study/Clinical Trial Completion Date:

Final Report Submission Date:

Other:

### **CMC:**

- Perform supplemental characterization of the MCB to provide additional assurance that the cell bank was (b) (4). These data should include the evaluation of (b) (4) (b) (4) analysis with respect to growth characteristics and product quality.

Final protocol Submission Date:

Study/Clinical Trial Completion Date:

Final Report Submission Date:

Other:

### **NON-CLINICAL:**

- Conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate time-points.

Final protocol Submission Date:  
Study/Clinical Trial Completion Date:  
Final Report Submission Date:  
Other:

APPEARS THIS WAY ON ORIGINAL

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/s/  
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KIM J ROBERTSON  
04/20/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Thursday, April 14, 2016 11:24 AM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA 761034: Tecentriq--GNE Inquiry on FDA Label comments

**Importance:** High

Hello Jerald---please see our responses below each query.

Kim

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Wednesday, April 13, 2016 10:15 PM  
**To:** Robertson, Kim  
**Subject:** BLA 761034: Tecentriq--GNE Inquiry on FDA Label comments

Hi Kim,

With regards to the label comments that were received on Tuesday April 12th, the team is currently reviewing FDA's comments and is planning to respond accordingly. However, upon receipt of the Warnings and Precautions sections (Section 5) we wanted to know if the Agency could help us to understand how the data numbers were generated? Specifically we had 2 inquiries:

1. Could the review division provide the pooled terms (i.e. list of PTs) used for the W&P terms:

- Pneumonitis (Section 5.1)
- Hepatitis (Section 5.2)
- Colitis (Section 5.3)
- Diarrhoea (Section 5.3)
- Hypothyroidism (Section 5.4, under Thyroid Disorders)
- Diabetes mellitus (Section 5.4, under Diabetes Mellitus)

Pneumonitis included pneumonitis and interstitial lung disease

Hepatitis included elevated transaminases, autoimmune hepatitis, hepatitis, liver disorder (the relevant patients were listed out in the comment to the applicant)

Colitis/diarrhea included diarrhea, colitis, frequent bowel movements, colitis microscopic, gastroenteritis, GI hypermotility

Hypothyroidism included hypothyroidism, increased TSH, and myxedema

Diabetes mellitus without an alternative etiology included diabetes and hyperglycemia, however [REDACTED] (b) (4) was removed.

2. For the AST, ALT and total bilirubin (Section 5.2): Could the Agency please clarify if the source of data was from AE or lab dataset?

For section 5.2, the lab section was used.

This clarity would be quite helpful to facilitate our review and prepare the GNE response.

Thanks,  
Jerald

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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KIM J ROBERTSON  
04/14/2016

**Robertson, Kim**

---

**From:** Robertson, Kim  
**Sent:** Wednesday, April 13, 2016 2:02 PM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA 761034; Tecentriq (atezolizumab)---T-Con Needed

Thank you Jerald. I will notify the team that the t-con is “a go”.

Relative to details, at MSKCC, the inspection found adverse events that were entered in the eCRFs, but **not included in the datasets**. This involved 3 of 30 pts enrolled on the Phase 2 trial at that site. These AEs occurred well before the data cutoff of May 5, 2015. The following AEs were not included in the datasets:

Subject 1236: Cholecystitis [4/2/15-4/6/15 ] **Grade 3 (SAE). Treatment interrupted.**  
LFT abnormalities and sepsis were reported, but cholecystitis was not reported.

Subject 1074: Right Shoulder Pain: [12/1/14- ongoing] Grade 1  
Chills: [10/2/14- 9/29/15] Grade 1

Subject 1202: UTI: [10/15/14-10/27/15] Grade 2  
Back Pain: [10/7/14- 10/27/14] Grade 2  
Headache: [10/21/14- no end] Grade 1  
Weakness: [10/21/14- no end] Grade 1  
Rash: [10/27/14- during infusion] Grade 2  
Weakness: [12/3/14- not resolved] Grade 1  
elevated AST: [12/9/14-12/16/14] **Grade 3**  
elevated ALT: [12/9/14-12/16/14] Grade 2

The team would like to know not only about Genentech’s process for moving AEs from the CRFs to the datasets, but also provide us with an estimate on how widespread this issue is.

Please use the following call-in information:

Local: 1-301-796-7777

Toll free: 1-855-828-1770

Follow the instructions that you hear on the phone.

Cisco Unified MeetingPlace **Meeting ID:** (b) (4)

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Wednesday, April 13, 2016 11:55 AM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq (atezolizumab)---T-Con Needed

Hi Kim,

Confirming that the proposed time (April 14th 3:30-4pm EST) works fine.

Please send any relevant details regarding the meeting as well as any items (if any) Genentech should be ready to discuss.

Thanks,  
Jerald

On Wed, Apr 13, 2016 at 8:13 AM, Jerald Grace <[gracej1@gene.com](mailto:gracej1@gene.com)> wrote:  
Hi Kim,

Let me discuss with the team. Should be fine. Will confirm ASAP

On Apr 13, 2016, at 6:03 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hello Jerald:

The clinical and OSI reviewers assigned to Genentech's BLA for Tecentriq (atezolizumab) need to have a brief t-con with Genentech. Is it possible that Genentech can avail itself to us for **Thursday, April 14, 2016; 3:30pm-4:0pm, EST**? The reason for the t-con is to discuss AEs that were found on inspection that were not included in the datasets.

Please let me know about Genentech's availability as soon as possible.

Thank you,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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KIM J ROBERTSON  
04/13/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Wednesday, April 13, 2016 9:43 AM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Vial and Carton Comments  
**Attachments:** BLA 761034 Container Carton Comments.docx

**Importance:** High

Hello Jerald:

Relative to Genentech's BLA for Tecentriq® (atezolizumab), please see the attached MS Word .doc, as it contains DMEPA and CMC comments pertinent to the vial and container.

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**BLA 761034/0**  
**Tecentriq (atezolizumab)**  
**Container Labels and Carton Labeling Comments**

We have the following comments regarding your proposed container labels and carton labeling submitted on January 12, 2016. Please respond by COB 4/20/2016.

**A. General Comments**

1. Replace "Tradename" with the conditionally approved proprietary name, Tecentriq.

**B. Carton Labeling**

1. Revise "(b) (4)" to "Single-Dose Vial". See the Agency's thinking on this issue (Selection of Appropriate Package Type Terms for Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>).

2. Revise the list of inactive ingredients to alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients. For example:

Vial contains in 20 mL: atezolizumab (1200 mg), glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg) and sucrose (821.6 mg).

Note deletion of the trailing zeros (62.0 mg to 62 mg and 8.0 mg to 8 mg).

3. Revise "(b) (4)" to "Product of Switzerland". This is our current labeling practice utilized when Applicants propose to label the Country of Origin.

**C. Vial Container Label**

1. On the principal display panel, ensure there is sufficient white space between the NDC number and the proprietary name to improve readability and to minimize information crowding.
2. See comments B1 and B3.

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KIM J ROBERTSON  
04/13/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Tuesday, April 12, 2016 5:12 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab) USPI---Complete Label  
**Attachments:** 12April16 Full Proposed Tecentriq (atezolizumab) USPI-complementary.docx

**Importance:** High

Hi Jerald:

Please see the attached MS Word .doc, as it is Genentech's USPI for Tecentriq® (atezolizumab) in its entirety, with DOP1 revisions and comments. Please review the label and provide us with a return label by **Friday, April 15, 2016, 3:30pm, EST**.

FYI.....the sections that were conveyed to Genentech on April 8, 2016 still contain the same revisions and/or comments, so they will be redundant.

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/12/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Friday, April 08, 2016 6:20 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab) USPI with FDA Revisions/Comments San HL and Sections 5 and 17  
**Attachments:** 08April16 - Tecentriq (atezolizumab) USPI Sans HL and Sections 5 and 17-complementary.docx  
**Importance:** High

Hello again Jerald:

Please see the attached MS Word document, as it is Genentech, Inc's. USPI for Tecentriq® (atezolizumab), with DOP 1 comments and revisions thus far.

**\*\*Please note**—The label does not include Highlights (HL) and Sections 5 and 17, as they are still being discussed by the Division. Upon the conclusion of our next Tecentriq® labeling meeting (**April 12<sup>th</sup>**), we will provide Genentech with a full label containing our remaining revisions and comments. We ask that Genentech reviews and return to us a full USPI, containing any of its comments/revisions, by **Friday, April 15, 2016, 3:00 pm EST**.

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/08/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Wednesday, April 06, 2016 4:23 PM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA 761034; Tecentriq (atezolizumab)--Promotional Materials

Thank you for the update Jerald. This update is most appreciative.

Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Wednesday, April 06, 2016 3:23 PM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq (atezolizumab)--Promotional Materials

Hi Kim,

I just spoke with my colleague overseeing the promotional pieces for Tecentriq and he informed me that most pieces are in but there are a few final pieces on track to be submitted by early next week.

He also informed me that he has a call with his FDA reviewer early Monday morning to update them on the outstanding items that will be submitted.

Hope this clarifies.

Regards,  
Jerald

On Wed, Apr 6, 2016 at 10:40 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hi Jerald:

I just had a conversation with the OPDP reviewer, who is reviewing Genentech's BLA for Tecentriq®, and she expressed to me her concern relative to the Promotional Materials for Tecentriq® and whether or not ALL of the promotional, labeling and advertisements, intended for dissemination or publication has been submitted. As a reminder, ALL of this

information needs to be submitted to the Agency during the pre-approval review stage of an application. Whatever is submitted prior to a *potential* approval of an application will be the ONLY promotional materials an applicant can use for **120-days** after a *potential* approval.

We **strongly** encourage Genentech to submit all of its promotional materials for Tecentriq® (atezolizumab) right away, because the Division intends to take a regulatory action much earlier than September, 2016.

Regards,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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KIM J ROBERTSON  
04/06/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Tuesday, April 05, 2016 4:14 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Additional Clinical Information Request

Hello again Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has an additional request for information:

### **ADDITIONAL CLINICAL INFORMATION REQUEST:**

We have reviewed the non-TCC bladder pts for PCD4989g and have the following question and requests for narratives:

We have already sent the following information requests:

**Pts 101006, 102103**

We have the following additional requests for information from review of non-TCC bladder pts in PCD4989g.

1. Pt 101606 developed gr 3 confusion. Please state the possible causes of this event.
2. Pt 102323 developed gr 4 respiratory failure, but had underlying breast cancer and no lung metastases. Please provide a narrative for this event.
3. Pt 101009 had gr 3 erythema. Please provide a narrative describing this event.
4. Pt 101006 had underlying renal cell carcinoma and a baseline creatinine of 1.23. On Day 483, Cr was 7.86 mg/dL. Please provide a narrative describing this event.
5. Please provide a narrative for the infusion reaction in pt 101103 on Day 28.
6. Please provide a narrative for pt 111209 with amyotrophy and pt 101210 with grade 2 myositis.
7. Please provide a narrative for pt 101102 with ulcerative keratitis and pt 111121 with keratitis.

Please provide us with a response to this query by **Tuesday, April 12, 2016, 3pm EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/05/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Tuesday, April 05, 2016 4:05 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Clinical Information Request

**Importance:** High

Hi Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has the following information request:

### **CLINICAL INFORMATION REQUEST:**

- We are concerned that since the (b) (4) pts on the IMvigor 211 trial are ongoing that these pts will be on study for a short time after this change and that the evaluation of TSH will be inadequate. Please provide additional information concerning the population and design of (b) (4). Please state when the milestones will be available for (b) (4).

Please provide us with a response to this query by **Thursday, April 7, 2016, 3pm EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
04/05/2016



BLA 761034

**MID-CYCLE COMMUNICATION**

Genentech, Inc.  
Attention: Jerald Grace, PharmD  
Associate Program Director  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Grace:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Tecentriq® (atezolizumab) Infusion, 60 mg/mL solution in a single use 20 mL vial.

We also refer to the teleconference between representatives of your firm and the FDA on March 23, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

V. Ellen Maher, MD  
Clinical Team Leader  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** March 23, 2016, 3:00pm-4:00pm EST

**Application Number:** 761034  
**Product Name:** Tecentriq® (atezolizumab) Infusion  
**Indication:** **Urothelial Bladder Cancer (UBC)**  
**Applicant Name:** Genentech, Inc.

**Meeting Chair:** V. Ellen Maher, MD, Clinical Team Leader  
**Meeting Recorder:** Kim J. Robertson, Regulatory Health Project Manager

**FDA ATTENDEES**

Geoffrey Kim, MD, Director, DOP1  
Amna Ibrahim, MD, Deputy Director, DOP1  
V. Ellen Maher, MD, Cross Discipline Team Leader, DOP1  
Yang-Min (Max) Ning, MD, PhD, Clinical Reviewer, DOP1  
Daniel Suzman, MD, Clinical Reviewer, DOP1  
Joel Welch, PhD, OPQ Application Team Lead, OBP  
Xianghong (Emily) Jing, PhD, Chemistry Reviewer, OBP  
Kim J. Robertson, Regulatory Health Project Manager, DOP1

**APPLICANT ATTENDEES**

Susan Andersen, Sr. Global Clinical Trial Leader  
Zachary Boyd, MS, Sr. Companion Diagnostic Manager, Oncology Biomarker Development  
Vandana Chauhan, MS, Regulatory Program Director, Pharma Technical Regulatory  
David Chonzi, MD, Safety Scientist Lead, Pharma Development Safety Risk Management  
Jerald Grace, PharmD, Associate Program Director, Product Development Regulatory  
Shi Li, PhD, Statistical Scientist, Biostatistics  
Sanjeev Mariathasan, PhD, Sr. Scientist, Biomarker sub-team leader, Oncology Biomarker Development  
Nathan McKnight, PhD, Technical Development Lead, Pharma Technical Development  
Flavia Di Nucci, MD, Sr. Safety Scientist, Pharma Development Safety Risk Management  
Josina Reddy, MD, PhD, Sr. Group Medical Director, Signaling Franchise Head, Product Development Oncology  
Mark Stroh, PhD, Senior Scientist, Clinical Pharmacology  
Melinda Teng, PhD, Sr. Statistical Scientist, Biostatistics  
AnnChristine Thastrom, MS, PhD, Clinical Scientist, Pharma Development Oncology, Clinical Development  
Kathie Winson, MS, Group Director, Product Development Regulatory

**Eastern Research Group Attendees:**  
Christopher A. Sese, Eastern Research Group, Inc.

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

### Clinical:

We have identified the following significant review issues. These may be able to be addressed via the following post-marketing requirements (PMRs):

- Develop a more sensitive assay for the assessment of neutralizing antibodies.
- Conduct a study which includes frequent assessment of thyroid function tests.  
*Discussion point: Genentech stated that they are obtaining TSH levels [REDACTED] (b) (4) [REDACTED] in an ongoing study. FDA stated this was insufficient and that further discussions will be needed.*
- Provide an assessment of long-term safety after 50 patients with advanced or metastatic bladder cancer has received atezolizumab for at least 1 year.  
*Discussion point: Genentech will provide a plan for a report on long-term safety.*

In addition, as a post-marketing commitment, we plan to ask that you provide additional follow up to determine the median duration of response in the IMvigor210 study.

Please note that our review is ongoing and we may have additional post-marketing requirements and commitments.

**CMC:**

- CMC informed Genentech that they needed to update their USPI regarding the storage time of 6 hours at 20–25°C and 24 hours at 2–8°C, for DP diluted in IV bags.

**Additional Discussion Points:**

- Genentech and the FDA further discussed clinical information requests relative to maximum grade of the Adverse Events (AE) per patient, prior to withholding the drug. The Agency would be looking at the same AEs, prior to withholding.
- The FDA wants to see Genentech’s proposal regarding AEs. All AEs pertinent to pneumonitis were discussed.
- The Agency is expecting Genentech’s response to its March 25, 2016, clinical information request by March 30, 2016, relative to the recurrence of the AE in patients re-challenged with atezolizumab following an immune-mediated adverse event or adverse event of special interest in which the dose was interrupted.
- The Agency asked Genentech to provide updated data as a Postmarketing Commitment (PMC), relative to median duration.

**3.0 INFORMATION REQUESTS**

**Non-Clinical:**

- Non-clinical information request dated March 10, 2016 with a March 22, 2016 reply date

**Clinical:**

- Clinical information requests dated March 15 and 18, 2016, both with a March 25, 2016 reply date
- Office of Safety Evaluation information request for a Pharmacovigilance Plan to be submitted to the BLA (if available)
- Clinical information request dated March 21, 2016 with a March 30, 2016 reply date.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

All major safety concerns can be addressed through review of the submission and the responses to our information requests. A REMS will not be required.

## **5.0 ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

## **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

The Late Cycle Meeting is currently planned for April 25, 2016; 3:00pm- 4:30pm, Eastern Standard Time. As stated in the Filing Communication, if major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 20, 2016.

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting is currently scheduled for April 25, 2016. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review. You may choose to cancel the Late Cycle Meeting, if you feel it is not needed, given our continued and regular communications. The PDUFA Action Date is September 12, 2016.

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/s/  
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KIM J ROBERTSON  
04/04/2016

VIRGINIA E MAHER  
04/05/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Friday, April 01, 2016 3:07 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)---Clinical Information Request

Hello Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has the following information request:

### **CLINICAL INFORMATION REQUEST:**

- Pt 234147-101006 had a gr 4 elevation in creatinine on day 483. The next creatinine level isn't until Day 708. Please provide a narrative concerning the adverse events associated with this increase in creatinine.

Please provide us with a response to this query by **Friday, April 8, 2016, 3:00pm EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
04/01/2016

**Robertson, Kim**

---

**From:** Robertson, Kim  
**Sent:** Thursday, March 31, 2016 2:10 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq--Clinical Information Request

**Importance:** High

Hello Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has the following requests for information:

**CLINICAL INFORMATION REQUEST:**

In the Safety Update for PCD4989g, you provided a narrative for patient 102103. This patient discontinued atezolizumab due to grade 3 amylase and lipase and required a prolonged course of steroids. Please provide the following:

1. The patient's symptoms at the time the increase in amylase and lipase were first noted and throughout the course of the laboratory abnormalities.
2. A statement concerning whether imaging that was done (such as a RUQ ultrasound or CT) to determine the cause of this elevation. If imaging was not done, please include this statement in the narrative.
3. Units for these laboratory abnormalities and a normal range
4. Information on other laboratories that may have been affected such as glucose or electrolytes (if nausea and vomiting occurred) throughout the course of the abnormal amylase and lipase.
5. The rationale for the decision to use a relatively low dose of prednisone, if available, would also be helpful.
6. Additional anti-cancer therapy after Day 294, if any

Please provide responses to these requests by **Friday, April 8, 2016, 3:00pm, EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1*

*Ofc. Phone: (301) 796-1441*

*Fax: (301) 796-9845*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
03/31/2016

## Robertson, Kim

---

**From:** Jerald Grace <grace.jerald@gene.com>  
**Sent:** Friday, March 25, 2016 2:15 PM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq--Clinical Information Request

Hi Kim,

Acknowledging receipt. Will send to team.

Jerald

On Fri, Mar 25, 2016 at 10:19 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hello again Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has a request for information:

### **CLINICAL INFORMATION REQUEST:**

Patients 4023 and 1006 experienced Grade 3 hypoglycemia on laboratory analysis. Neither of these patients was on insulin and discussion of these events is not provided in their respective narratives. Please provide additional data including concomitant illness and medications regarding these events.

Please provide this information by **Wednesday, March 30, 2016, 3:00pm, EST.**

Regards,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:(301)796-1441)*

*Fax: [\(301\) 796-9845](tel:(301)796-9845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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/s/  
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KIM J ROBERTSON  
03/25/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Thursday, March 24, 2016 2:58 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab) --Clinical Information Request

Hello Jerald:

Relative to Genentech, Inc.'s Original BLA for Tecentriq (atezolizumab), the clinical reviewer has the following requests for information:

### **CLINICAL INFORMATION REQUEST:**

- For Study G029293, provide your updated DV tabulation dataset from which the protocol violation information was generated and reported in the newly submitted ADSL dataset (with the cutoff date of 11/27/2015). We noted that the number of patients with major protocol violations reported in this ADSL dataset are lower than the number (63) of major violations reported in the DV tabulation dataset (with the cutoff date of September 15, 2015). Please address the discrepancy and conduct an analysis to assess whether the protocol violations affect the reported efficacy and safety results in Cohort 2 of the Phase 2 study.
- Regarding the reported origin of tumor specimens (metastasis vs. primary lesions) that were used for determination of PD-L1 IC scores, please address the following issues:
  - 1) The number of patients whose metastatic specimens were used in the PD-L1 assay. Our evaluation of your datasets (submitted to the CDER) showed that 85 patients had their PD-L1 IC scores determined with metastatic tumor slides and the rest of patients with primary tumor slides. However, the information submitted to the CDRH showed that 78 patients had metastatic tumor specimens used for the reported PD-L1 IC assay. Please address the discrepancy and provide the ID number of patients that caused the difference. Also, provide a tabular list to show the distribution of patients' tumor specimens used in the central laboratory by archived primary specimens, archived metastatic specimens, and newly obtained tumor specimens for study entry.
  - 2) For patients whose primary tumor slides were used for determination of PD-L1 IC scores, clarify whether they had evidence of metastases at the time of obtaining the primary tumor specimens. Provide patients' ID number as indicated.

3) Clarify the three reported Biopsy Types: BIOPSY, RESECTION, and TURBT. It is not clear to reviewers what differences existed between BIOPSY and TURBT in collecting primary tumor specimens or whether “RESECTION” represented surgical removals of the organs containing the primary tumors or metastatic tumors.

Please provide us with responses to address this request no later than **Monday, April 04, 2016, 2pm EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
03/24/2016

**Robertson, Kim**

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**From:** Robertson, Kim  
**Sent:** Thursday, March 24, 2016 3:05 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab) --Clinical Comment/Information Request  
**Importance:** High

Hello again Jerald:

Relative to Genentech, Inc.'s Original BLA for Tecentriq (atezolizumab), the clinical reviewer has the following comment/request for information:

**CLINICAL COMMENT/ INFORMATION REQUEST:**

Examination of hyper and hypothyroidism on atezolizumab:

Our understanding is that you plan assess TSH [REDACTED] (b) (4) in an ongoing study and that a substantial number of patients have had thyroid testing at baseline and end of study.

With similar medications, the incidence of hyperthyroidism varies between 1.8-3.3% and hypothyroidism between 6.9-8.1%. Extrapolating this information to atezolizumab, this would result in [REDACTED] (b) (4) would be insufficient to accurately examine the course (or incidence) of thyroid disease. Please provide a plan to measure TSH at least every 6 weeks in a larger number of patients. It is not necessary that this study be conducted in patients with bladder cancer.

Please provide a response to this request by **Monday, April 04, 2016, 2pm EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
03/24/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Monday, March 21, 2016 5:14 PM  
**To:** 'Jerald Grace'  
**Subject:** RE: BLA 761034; Tecentriq (atezolizumab)--Clinical Information Request

Hello Jerald:

The clinical reviewer has informed me that the inclusion of the databases that you have mentioned is acceptable.

Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [<mailto:grace.jerald@gene.com>]  
**Sent:** Monday, March 21, 2016 5:10 PM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq (atezolizumab)--Clinical Information Request

Thanks Kim

On Mon, Mar 21, 2016 at 1:50 PM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

I will inform the requesting physician about GNE's clarifying question and let you know of his response as soon as I know.

Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

**From:** Jerald Grace [mailto:[grace.jerald@gene.com](mailto:grace.jerald@gene.com)]

**Sent:** Monday, March 21, 2016 3:53 PM

**To:** Robertson, Kim

**Subject:** Re: BLA 761034; Tecentriq (atezolizumab)--Clinical Information Request

Hi Kim,

Acknowledging receipt and wanted to get some clarity on one point.

The first part of the request mentions an outcome of patients **across the atezolizumab database**--We plan to focus this response on the patients included within the safety update (FIR, POPLAR, BIRCH, PCD4989g and IMvigor 210). Is this acceptable?

This clarity would help us generate the best analysis for the response.

Regards,

Jerald

On Mon, Mar 21, 2016 at 10:26 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hi Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has the following request for information:

**CLINICAL INFORMATION REQUEST:**

- Provide an analysis of the outcome of patients across the atezolizumab database and within the UBC database with regard to recurrence of the AE in patients re-challenged with atezolizumab following an immune-mediated adverse event or adverse event of special interest in which the dose was interrupted. Please break this down by Grade 1-4 of the initial IMAE/AESI and by Grade 3-4.

Please provide us with a response to this IR by **Wednesday, March 30, 2016, 3:00pm EST.**

Regards,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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/s/  
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KIM J ROBERTSON  
03/21/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Monday, March 21, 2016 1:26 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Clinical Information Request

Hi Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has the following request for information:

### **CLINICAL INFORMATION REQUEST:**

- Provide an analysis of the outcome of patients across the atezolizumab database and within the UBC database with regard to recurrence of the AE in patients re-challenged with atezolizumab following an immune-mediated adverse event or adverse event of special interest in which the dose was interrupted. Please break this down by Grade 1-4 of the initial IMAE/AESI and by Grade 3-4.

Please provide us with a response to this IR by **Wednesday, March 30, 2016, 3:00pm EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
03/21/2016

**PeRC Meeting Minutes  
March 2, 2016**

**PeRC Members Attending:**

Lynne Yao  
Hari Cheryl Sachs  
Linda Lewis  
Thomas Smith  
Meshawn Payne  
Dianne Murphy  
Gerri Baer  
Wiley Chambers  
Lily Mulugeta  
Peter Starke  
Gil Burckart  
Raquel Tapia  
Greg Reaman  
Dionna Green  
Michelle Roth-Kline  
Robert Skip Nelson  
John Alexander  
Ruthie Davi  
Colleen Locicero  
Gettie Audain  
Shrikant Pagay

NON-RESPONSIVE

**Agenda**

NON-RESPONSIVE



	BLA 761034	Tecentriq (atezolizumab) Full Waiver with Agreed iPSP	DOP1	Kim Robertson	Metastatic Urothelial Bladder Cancer
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NON-RESPONSIVE



4 Pages have been withheld in full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

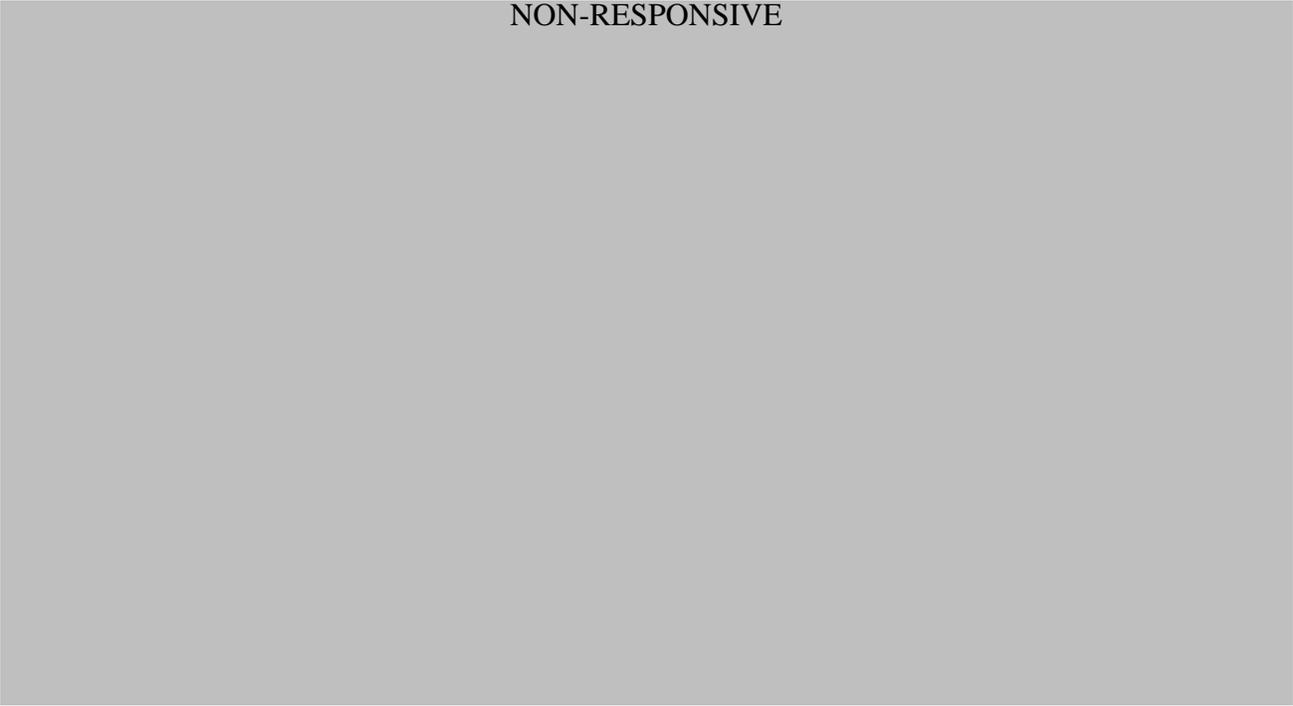


**Tecentriq (atezolizumab) Full Waiver with Agreed iPSP**

- Proposed Indication: Metastatic Urothelial Bladder Cancer

- *PeRC Recommendations:*
  - The PeRC concurred with the Agreed iPSP

NON-RESPONSIVE



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MESHAUN L PAYNE  
03/17/2016

## Robertson, Kim

---

**From:** Robertson, Kim  
**Sent:** Thursday, March 17, 2016 1:51 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--OSE Information Request  
**Attachments:** FDA Guidance.Good PV Practices and PE Assessment.2005.pdf; FDA Guidance.E2E PV Planning.2005.pdf

Hi Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), our OSE colleagues have the following request for information:

### **OSE INFORMATION REQUEST:**

The FDA encourages sponsors/applicants to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with atezolizumab following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please submit it as an amendment to the BLA application.

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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# **Guidance for Industry**

## **E2E Pharmacovigilance Planning**

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

**April 2005  
ICH**

# Guidance for Industry

## E2E Pharmacovigilance Planning

*Additional copies are available from:*

*Office of Training and Communication  
Division of Drug Information, HFD-240  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
(Tel) 301-827-4573  
<http://www.fda.gov/cder/guidance/index.htm>*

*Office of Communication, Training and  
Manufacturers Assistance, HFM-40  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike, Rockville, MD 20852-1448  
<http://www.fda.gov/cber/guidelines.htm>.  
(Tel) Voice Information System at 800-835-4709 or 301-827-1800*

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

**April 2005  
ICH**

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

### **E2E Pharmacovigilance Planning**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- Safety specification
- Pharmacovigilance plan
- Annex — Pharmacovigilance Methods

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

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

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

The following principles underpin this guidance:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The worldwide experience should be briefly discussed, including:

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

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

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

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

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

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

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

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

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

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

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

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

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

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### e. Epidemiology

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

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

### f. Pharmacological class effects

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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**IV. REFERENCES (4)**

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

## **ANNEX — PHARMACOVIGILANCE METHODS**

### **1. Passive Surveillance**

- **Spontaneous Reports**

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

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

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

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

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- **Case Series**

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

### **2. Stimulated Reporting**

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

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

### **3. Active Surveillance**

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

- **Sentinel Sites**

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

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

- **Drug Event Monitoring**

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

- **Registries**

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

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

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

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

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

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

- **Case-control Study**

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

- **Cohort Study**

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

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

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

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

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

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

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

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

### **6. Descriptive Studies**

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

- **Natural History of Disease**

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

- **Drug Utilization Study**

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

## *Contains Nonbinding Recommendations*

### **REFERENCES**

1. ICH Guidance E2D; Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting, 3.1.1 Spontaneous Reports.
2. Pinkston V, Swain EJ, Management of adverse drug reactions and adverse event data through collection, storage, and retrieval. In Stephens MDB, Talbot JCC, and Routledge PA, eds. *Detection of New Adverse Drug Reactions*. 4<sup>th</sup> ed. 1998; MacMillan Reference Ltd, London. p 282.
3. Faich GA, U.S. adverse drug reaction surveillance 1989 – 1994. *Pharmacoepidemiology Drug Safety* 1996; 393-398.
4. Goldman SA, Limitations and strengths of spontaneous reports data. *Clinical Therapeutics* 1998; 20 (Suppl C):C40-C44.
5. Hartmann K, Doser AK, Kuhn M, Postmarketing safety information: How useful are spontaneous reports. *Pharmacoepidemiology and Drug Safety* 1999; 8:S65-S71.
6. “Responding to Signals” Waller PC and Arlett PA, in *Pharmacovigilance*, Editor Mann RD, John Wiley and Sons Ltd 2002.
7. DuMouchel W, Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting system. *Am Stat* 1999; 53:177-190.
8. Bate A, Lindquist M, Edwards IR, A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacology* 1998; 54:315-321.
9. Van Puijenbroek E, Egberts ACG, Heerdink ER, Leufkens HGM, Detecting drug-drug interactions using a database for spontaneous adverse drug reactions: An example with diuretics and non-steroidal anti-inflammatory drugs. *Eur J Clin Pharmacol* 2000; 56:733-738.
10. Venning GR, Identification of adverse reactions to new drugs. III: Alerting processes and early warning systems. *BMJ* 1983; 286:458-460.
11. Edwards IR, The management of adverse drug reactions: From diagnosis to signal. *Thérapie* 2001; 56:727-733.
12. In Strom BL (ed.). *Pharmacoepidemiology*, 3<sup>rd</sup> ed. 2002; John Wiley and Sons, Ltd, New York, NY.
13. Mitchell AA, Van Bennekom CM, Louik C, A pregnancy-prevention program in women of childbearing age receiving isotretinoin. *N Engl J Med* (1995 Jul 13); 333(2):101-6.

*Contains Nonbinding Recommendations*

14. Task Force on Risk Management. Report to the FDA Commissioner. Managing the risks from medical product use: Creating a risk management framework. Part 3. How does FDA conduct postmarketing surveillance and risk assessment. May 1999.
15. In Mann RD and Andrews EB (eds.) Pharmacovigilance 2002, John Wiley and Sons, Ltd, West Sussex, England.
16. Coulter DM, The New Zealand intensive medicines monitoring programme in pro-active safety surveillance. *Pharmacoepidemiology and Drug Safety* 2000; 9:273-280.
17. Mackay FJ, Post-marketing studies. The work of the Drug Safety Research Unit. *Drug Safety* 1998;19: 343-353.
18. Garcia Rodriguez LA, Perez Gutthann S, Use of the UK General Practice Research Database for Pharmacoepidemiology. *Br. J Clin Pharmacol* 1998; 45:419-425.

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# Guidance for Industry

## Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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

**March 2005  
Clinical Medical**

# Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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Food and Drug Administration  
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# Guidance for Industry<sup>1</sup>

## Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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

### I. INTRODUCTION

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

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

### II. BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Good case reports include the following elements:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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<sup>23</sup> Ibid.

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

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

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

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

### **B. Registries**

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

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

Registries can be particularly useful for:

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

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

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

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

<sup>27</sup> Ibid.

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

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

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

### **C. Surveys**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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/s/  
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KIM J ROBERTSON  
03/17/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Tuesday, March 15, 2016 12:30 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Clinical Information Request

Hello Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), the clinical reviewer has the following request for information:

### **CLINICAL INFORMATION REQUEST:**

- Please provide an analysis of Urinary Tract Infection (including the preferred terms: UTI bacterial, UTI pseudomonal, Urosepsis, Kidney infection, Cystitis, Pyelonephritis) by whether there was sterile pyuria or whether a urinary pathogen was either cultured or present at >100k cfu/ml in a urine specimen.
- Please provide a narrative for Cohort 2 Patient ID 1167.

Please provide us with responses to address this request for information by **Friday, March 25, 2016, 3pm EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
03/15/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Friday, March 11, 2016 2:18 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Filing Status  
**Attachments:** Final No Filing Review Issues Identified 74 Day Letter BLA 761034 Tecentriq (atezolizumab) (COR-NDAFILE-05)(COR-SNDAFILE-05)(COR-BLAFILE-05)( COR-SBLA.pdf

**Importance:** High

Hello Jerald:

Please see the attached .pdf document, as it pertains to Genentech, Inc.'s Original BLA for Tecentriq® (atezolizumab) Infusion, 60 mg/mL solution in a single use 20 mL vial and its filing status.

Relative to the Tecentriq® (atezolizumab) PI, please note that there are two PLR content and format issues that we will need corrected (refer to the letter). There were two additional PLR issues that were inadvertently left out of the letter, but require correction and they are as follows:

### **ADDITIONAL PLR CORRECTIONS NEEDED:**

- Superscript the Registered Sign (®) following the product name.
- The Medication Guide needs to start on a new page to avoid the information starting halfway the page.

We will need an updated PI sent back to us, with the PLR corrections made, no later than **Wednesday, March 16, 2016, 4:00pm EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
03/11/2016



BLA 761034

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Genentech, Inc.  
Attention: Jerald Grace, PharmD  
Associate Program Director  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Grace:

Please refer to your Biologics License Application (BLA) dated January 12, 2016, received January 12, 2016, submitted under section 351(a) of the Public Health Service Act for Tecentriq® (atezolizumab) Infusion, 60 mg/mL solution in a single use 20 mL vial.

We also refer to your amendment dated February 24, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is September 12, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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

April 20, 2016. This date conforms to the 21<sup>st</sup> Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is March 18, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

### **PRESCRIBING INFORMATION**

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. A horizontal line must separate the Table of Contents (TOC) from the Full Prescribing Information (FPI). Please include a horizontal line separating these two sections from one another.
2. White space should be present before each major heading in Highlights (HL). Please insert the necessary white space.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 16, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

### **PROMOTIONAL MATERIAL**

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 601.45, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administrations 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 reference the waiver granted on September 11, 2015, for the pediatric study requirement for this application.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

Amna Ibrahim, MD  
Deputy Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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AMNA IBRAHIM  
03/11/2016

**Robertson, Kim**

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**From:** Robertson, Kim  
**Sent:** Thursday, March 10, 2016 2:32 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034 Tecentriq (atezolizumab)--Non Clinical Information Request  
**Importance:** High

Hello again Jerald:

Relative to GNE's Original BLA for Tecentriq® (atezolizumab), my non-clinical reviewers have ascertained the following request for information:

**NON-CLINICAL INFORMATION REQUEST:**

1. In the pr [redacted] dicated that studies were [redacted] (b) (4),  
ongoing [redacted]. Provide a status update on  
these st [redacted] usly discussed, we  
acknowledge that these studies will not be available for review with this BLA  
submission.
2. If available, provide the suspected mechanism for the effects of atezolizumab on  
menstruation in Cynomolgus monkeys.
3. [redacted] (b) (4)  
[redacted]  
[redacted]

Please provide us with responses to address these queries by **Tuesday, March 22, 2016, 1:00pm EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845*

Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)

APPEARS THIS WAY ON ORIGINAL

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/s/  
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KIM J ROBERTSON  
03/10/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Wednesday, March 09, 2016 5:07 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq--QT-IRT Request

**Importance:** High

Hello Jerald:

Relative to Genentech's Original BLA for Tecentriq®, my QT-IRT colleagues have the following request:

### **QT-IRT INFORMATION REQUEST:**

- The ECG waveforms for Study PCD4989g have no annotations in the ECG warehouse, so we are unable to determine the quality of the measurements. Please resubmit those waveform files with annotations to the ECG warehouse.

Thanks,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
03/09/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 761034

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990

ATTENTION: Jerald Grace, Pharm.D.  
Regulatory Project Management

Dear Dr. Grace:

Please refer to your Biologics License Application (BLA) dated January 12, 2016, received January 12, 2016, submitted under section 351(a) of the Public Health Service Act for Atezolizumab, 60 mg/mL.

We also refer to your December 18, 2015, correspondence, received December 18, 2015, requesting review of your proposed proprietary name, Tecentriq.

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

If any of the proposed product characteristics as stated in your December 18, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Kim Robertson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, 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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LUBNA A MERCHANT on behalf of TODD D BRIDGES  
03/08/2016

**Robertson, Kim**

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**From:** Robertson, Kim  
**Sent:** Tuesday, March 08, 2016 1:12 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** New BLA 761034; Tecentriq (atezolizumab)---Clinical Pharmacology IR  
**Importance:** High

Hi Jerald:

Relative to GNE's newly submitted BLA for Tecentriq® (atezolizumab), my clinical reviewer has the following request for information:

**CLINICAL PHARMACOLOGY REQUEST FOR INFORMATION:**

- Please provide an analysis for incidence of AE grade  $\geq 3$  by ATA status and incidence of AE grade  $< 3$  by ATA status for Studies IMvigora 210 and PCD4989g. The analysis results can be reported in the similar format as Table 35, Summary of Clinical Safety (Section 2.7.4)

**Please provide us with a response to this IR by Thursday, March 10, 2016, 3:00pm EST.** Please also provide us with a courtesy e-mail copy of your response to the IR for ease of dissemination to the requestor.

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
03/08/2016

**Robertson, Kim**

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**From:** Robertson, Kim  
**Sent:** Friday, March 04, 2016 10:31 AM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)---Clinical IR

**Importance:** High

Hello Jerald:

Relative to Genentech's newly submitted BLA for Tecentriq® (atezolizumab), the clinical reviewer has the following requests for information:

**CLINICAL INFORMATION REQUEST:**

Please provide narratives for the patients in Cohort 2 who received corticosteroids without corresponding AEs that contain details regarding the following events:

268261-1104: Hydrocortisone 10mg for skin irritation  
268261-1118: Dexamethasone 2mg for nausea and vomiting  
268833-1082: Hydrocortisone 20mg for adrenal insufficiency and 10mg for rosacea  
269137-7001: Dexamethasone 8mg for "worsening condition"  
269145-1106: Cortisone 10mg for sciatic nerve pain

For patient 268833-1082, please clarify whether an ACTH stimulation test was performed and whether the investigator determined an etiology of adrenal insufficiency (including prior corticosteroid use or immune-mediated). Provide data regarding any adrenal imaging performed.

Please provide your responses to this IR by **Thursday, March 17, 2016, 4:00pm EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
03/04/2016

**Robertson, Kim**

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**From:** Robertson, Kim  
**Sent:** Monday, February 29, 2016 2:45 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Pharmacometrics Information Request

**Importance:** High

Hi Jerald:

Relative to Genentech's Original BLA for Tecentriq® (atezolizumab), my pharmacometrics reviewer has the following request for information:

**PHARMACOMETRICS INFORMATION REQUEST:**

Reference is made to your report titled "Pop PK Report 1066935":

- Explore the effect of ATA on clearance in PPK analysis by treating ATA as time-varying covariates.
- Submit all relevant datasets and control streams for the above analysis

Refer to the pharmacometric data submission guidelines

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm18048.htm>) for more information.

Please provide us with responses to the request by **Friday, March 4, 2016; 3:30pm, EST.**

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
02/29/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Monday, February 22, 2016 4:24 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 7961034; Tecentriq (atezolizumab)--Clinical Pharmacology Information Request  
**Attachments:** 22February16 OCP IR.docx

**Importance:** High

Hello Jerald:

Relative to Genentech's new BLA for Tecentriq (atezolizumab), my clinical pharmacology reviewers have ascertained the following request for information, as contained in the attached Word .document.

Please review the document and provide us with your responses to the questions by **Friday, February 26, 2016; 3:00pm, EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

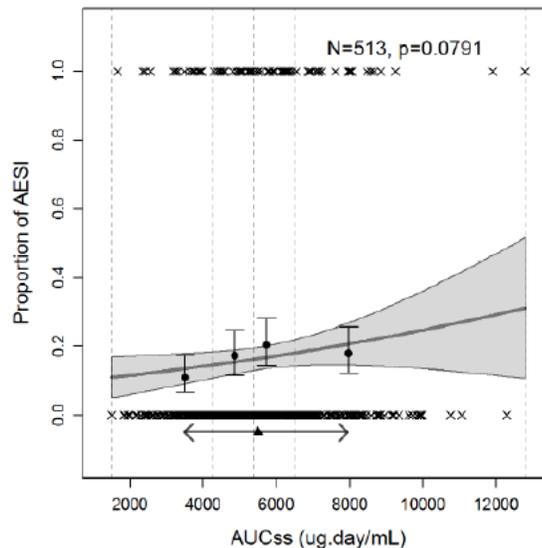
## Questions

1. In page 417 of 2.7.4 Summary of Clinical Safety (see table below), the reported proportion of AESI of all UBC (N=521) is <sup>(b) (4)</sup> %.



In Figure 10 of the 2.7.2 Summary of Clinical Pharmacology Studies (see Figure 10.blow), the proportion of AESI of 513 mBC patients, a subset of the 521 UBC patients with PK data, seems less than 20%. Please clarify <sup>(b) (4)</sup> difference between AESI proportions in above table and Figure 10.

Figure 10 Proportion of Patients Experiencing AESI from Studies PCD4989g (Urothelial Carcinoma Cohort) and IMvigor 210 (Cohorts 1 and 2) for Atezolizumab Doses 15 mg/kg and 1200 mg q3w



AUC<sub>ss</sub>=AUC at steady-state; AESI=adverse event of special interest; N=number of patients; p=p value of Wald test in logistic regression of incidence versus exposure; q3w= every three weeks.

Note: The thick solid line and shaded area represent the logistic regression slope model and 95% prediction interval. The filled circles and error bar represent the incidence in exposure quartiles and 95% CI. The vertical lines are the limits of the exposure quartiles. The cross is AE events (0: No, 1: Yes). The triangle and two-headed arrow represent the mean exposure and exposure interval between the 10th and the 90th percentile for patients receiving 1200 mg atezolizumab, respectively.

Source: ER Report

2. Please provide a mean ( $\pm$ SD) serum atezolizumab concentration vs time profile and related data for all Cycles by dose group (PK-evaluable population) for Study PCD4989g.

3. Please provide individual subject PK parameters (as those listed on Table 11.4.1.2-3 and Table 11.4.1.2-4 of report “CSR JO28944: Phase I Study of MPDL3280A in Patients with Advanced Solid Tumors”) in xpt format for Study JO28944.
4. Reference is made to your report titled “EXPOSURE-RESPONSE ANALYSIS REPORT (1067242)”. Conduct the following analysis and submit your results by 2/26/2016.
  - a. E-R analysis for ORR using multivariate analysis.
  - b. E-R analysis for safety endpoints for grade 1-2 AE and AESI . All related datasets and code/control streams should be also be submitted along with the above analysis. Define file explaining the dataset and codes should be included.Refer to the pharmacometric data submission guidelines (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm18048.htm>) for more information.

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KIM J ROBERTSON  
02/22/2016

**Robertson, Kim**

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**From:** Robertson, Kim  
**Sent:** Tuesday, February 16, 2016 4:16 PM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)---Pharmacometrics IR

**Importance:** High

Hello Jerald:

Our pharmacometrics reviewer for GNE's BLA for Tecentriq has the following request for information:

**PHARMACOMETRICS REQUEST FOR INFORMATION:**

Reference is made to your report titled "EXPOSURE-RESPONSE ANALYSIS REPORT (1067242)". Please conduct the following analyses:

- a. E-R analysis for ORR/DOR using multivariate analysis.
- b. E-R analysis for safety endpoints for grade 1-2 AE and AESI .

All related datasets and code/control streams should be also be submitted along with the above analysis. Define file explaining the dataset and codes should be included.

Refer to the pharmacometric data submission guidelines (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm18048.htm>) for more information.

Please submit your results for theses analyses and submit them by **Tuesday, February 23, 2016, 3:00pm EST.**

Regards,  
Kim

*Kim J. Robertson  
Regulatory Health Project Manager  
Food and Drug Administration  
Division of Oncology Products 1  
Ofc. Phone: (301) 796-1441  
Fax: (301) 796-9845  
Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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KIM J ROBERTSON  
02/16/2016

## Robertson, Kim

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**From:** Jerald Grace <grace.jerald@gene.com>  
**Sent:** Friday, February 12, 2016 11:42 AM  
**To:** Robertson, Kim  
**Subject:** Re: BLA 761034; Tecentriq (atezolizumab)--ClinPharm and Cardiac Safety Table  
**Attachments:** 20160212-clin-resp-fda-req-info.pdf

Hi Kim,

As requested, please see attached for the info on the ECG waveforms, received 3 Feb 2016. This will formally be submitted to BLA 761034 today as well.

Let me know if you have any questions.

Regards,  
Jerald

On Wed, Feb 3, 2016 at 6:43 AM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Thanks Jerald. I will forward this to the reviewers who are requesting it. Actually, those reviewers do have an additional request.....

Please submit all related ECG waveforms to the ECG warehouse at [www.ecgwarehouse.com](http://www.ecgwarehouse.com). IF for some reason GNE has already done this as well, please let me know, so that I may inform the group that is asking.

Thank you Jerald,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:(301)796-1441)*

*Fax: [\(301\) 796-9845](tel:(301)796-9845)*

Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)

**From:** Jerald Grace [mailto:[grace.jerald@gene.com](mailto:grace.jerald@gene.com)]

**Sent:** Tuesday, February 02, 2016 3:17 PM

**To:** Robertson, Kim

**Subject:** Re: BLA 761034; Tecentriq (atezolizumab)--ClinPharm and Cardiac Safety Table

Hi Kim,

I share your sentiments. Definitely a pleasure conversing with you and the FDA review team on the mUC program once again. As always, thanks for all of your assistance during our visit!

With regards to the request for the the Highlights of Clinical Pharmacology and Cardiac Safety table, this document was provided in the mUC BLA 761034 submission on January 12 2016. The document can be found in Module 5 under **5.3.5.2 Study Reports of Uncontrolled Clinical Studies**. I have also attached a copy of the document to this email for your convenience.

Please let me know if there is any additional questions on this request.

Regards,

Jerald

On Tue, Feb 2, 2016 at 1:58 PM, Robertson, Kim <[Kim.Robertson@fda.hhs.gov](mailto:Kim.Robertson@fda.hhs.gov)> wrote:

Hi Jerald:

Hopefully, you're back on your warm coast trying to unpack and dust off any snow residue you might've collected on your shoes while visiting our fair city. ☺ Please allow me to say that it was indeed a pleasure to see you and your colleagues yesterday. It was so very nice to have made the acquaintance of those I did not know as well.

Please see the attached Word .doc, as it is a Highlights of Clinical Pharmacology and Cardiac Safety Table that we need GNE to complete, relative to BLA 761034; Tecentriq (atezolizumab). Please complete and return to me no later than

**Friday, February 5, 2016.**

Regards,

Kim

*Kim J. Robertson*

*Regulatory Health Project Manager*

*Food and Drug Administration*

*Division of Oncology Products 1*

*Ofc. Phone: [\(301\) 796-1441](tel:3017961441)*

*Fax: [\(301\) 796-9845](tel:3017969845)*

*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

--

Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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Jerald Grace, PharmD | Associate Program Director | Product Development Regulatory (PDR) |  
Genentech, Inc. | 1 DNA Way, South San Francisco, CA. 94080 | (b) (6)  
(mobile) | [grace.jerald@gene.com](mailto:grace.jerald@gene.com) |

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KIM J ROBERTSON  
02/12/2016

## Robertson, Kim

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**From:** Robertson, Kim  
**Sent:** Wednesday, February 03, 2016 10:10 AM  
**To:** Jerald Grace (grace.jerald@gene.com)  
**Subject:** BLA 761034; Tecentriq (atezolizumab)--Information Request

**Importance:** High

As promised Jerald, please see the following, as this is our request for additional information following the February 02, 2016 AOM and Technical Walk-Through Meetings, relative to Genentech's Original BLA Application for Tecentriq:

Please provide a timeline for the submission of each request:

1. Please provide an analysis of AEs (all-cause all-grade and Grade 3+) by prior lines of therapy. Please break line of therapy into 2<sup>nd</sup> line vs 3<sup>rd</sup>+ line.
2. Provide data and narratives on AEs treated with non-corticosteroid immunomodulatory agents.
3. Provide data regarding extent of disease in subjects who experienced a complete response.
4. Slide # 27 from the Applicant Orientation Meeting showed that in your Phase 2 trial, the number of responders [REDACTED] (b) (4) Please provide the IRC and Genentech's explanation of this [REDACTED] (b) (4) Include, in tabular format, investigator and IRC [REDACTED] (b) (4) tumor measurements at each time point.
5. Please provide an analysis of discordance in terms of time and type of response between the investigator and IRC for PCD4989g.
6. Please provide an analysis of the correlation of tumor response, PD-L1 IHC status, and the extent of infiltrating lymphocytes surrounding the tumor. Please provide the criteria you used to quantify the extent of lymphocytic infiltration.
7. We note that 61% of patients entered the study > 3 months after their most recent chemotherapy. Please clarify whether these patients had evidence of progression after their most recent chemotherapy and prior to study entry.
8. Please provide the DMC meeting minutes communicated to Genentech by February 11.
9. Our understanding is that the updated data that you will provide in February 2016 does not provide as estimate of the median duration of response in PCD4989g or in ImVigor210. Please provide an estimate of when this data will be available in all treated, PD-L1 IHC 0, PD-L1 IHC 1, 2, and 3, and PD-L1 IHC 2/3.
10. Provide the SAS program used to derive the response status from raw data (target lesion measurements, non-target status, and new lesion status at each assessment) following RECIST v1.1 based on investigator and IRF assessments. This program should be stand-alone (i.e., no

macros) so that it can be run on FDA computers. Please also submit an output dataset (one record per patient per tumor assessment) including the following data:

- Patient ID, Randomized arm, Visit number, Visit name, Visit date, Baseline target lesion SLD, Target lesion SLD at this visit, % change of SLD from baseline, Nadir SLD value, % change of SLD from nadir, Non-target lesion response status at this visit, New lesion (yes/no) at this visit, Response status at this visit, Best overall response, Evaluator (Investigator or IRF)

11. Provide your analyses of CR/PR in the following patient groups based on the updated response datasets in September of 2015: Patients who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy; Patients with non-bladder urothelial carcinoma at study entry; Patients with visceral and/or bone metastases.
12. Specify patients who had responses in metastatic lesions in the liver, lungs, and bone. Also, list patients who were enrolled in Cohort 2 of G029293 due to bone metastasis progression and patients who came off the study secondary to evidence of bone metastasis progression detected during the study.
13. Provide brief narratives to clarify why, in the updated analysis, Subject G029293-269145-1008 was reassigned to Cohort 2, and G029293-270306-4024 and G029293-272905-1279 to Cohort 1.

Regards,  
Kim

*Kim J. Robertson*  
*Regulatory Health Project Manager*  
*Food and Drug Administration*  
*Division of Oncology Products 1*  
*Ofc. Phone: (301) 796-1441*  
*Fax: (301) 796-9845*  
*Email: [kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)*

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/s/  
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KIM J ROBERTSON  
02/03/2016



BLA 761034

**BLA ACKNOWLEDGMENT**

Genentech, Inc.  
Attention: Jerald Grace, PharmD  
Associate Program Director  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Grace:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Tecentriq® (atezolizumab)

Date of Application: January 12, 2016

Date of Receipt: January 12, 2016

Our Reference Number: BLA 761034

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 March 12, 2016, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) 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. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

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

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

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

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

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

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 761034** submitted on January 12, 2016, and that it contains the FDA Form 3674 that was to accompany that application.

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

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 1  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

Kim J. Robertson  
Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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KIM J ROBERTSON  
01/26/2016



IND 120827

**MEETING MINUTES**

Genentech, Inc.  
Attention: Jerald Grace, PharmD  
Regulatory Program Management  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Grace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for atezolizumab (MPDL3280A).

We also refer to the teleconference between representatives of your firm and the FDA on September 24, 2015. The purpose of the meeting was to discuss and reach agreement on the acceptability of clinical trial results from pivotal phase 2 study GO29293 to form the basis of the BLA for the proposed UBC indication.

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

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

V. Ellen Maher, MD  
Clinical Team Leader  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre BLA

**Meeting Date and Time:** September 24, 2015, 11:00am-12:00pm  
**Meeting Location:** White Oak Building #22, Conf. Room 1421 (teleconference)

**Application Number:** 120827  
**Product Name:** atezolizumab (MPDL3280A)  
**Indication:** urothelial bladder cancer (UBC)  
**Sponsor/Applicant Name:** Genentech

**Meeting Chair:** V. Ellen Maher, MD  
**Meeting Recorder:** Kim J. Robertson

**FDA ATTENDEES**

Geoffrey S. Kim, MD, Director, DOP 1  
V. Ellen Maher, MD, Clinical Team Leader, DOP 1  
Yang-Min (Max) Ning, MD, Ph.D., Clinical Reviewer, DOP 1  
Shenghui Tang, Ph.D., Biometrics Team Leader, DBV  
Erik Bloomquist, Ph.D., Biometrics Reviewer, DBV  
Joel Welch, Ph.D., Lead Chemist, OBP  
Xianghong (Emily) Jing, Ph.D., Chemistry Reviewer, OBP  
Janaki Veeraraghavan, Ph.D., Reviewer, OIR/CDRH  
Kim J. Robertson, Regulatory Health Project Manager, DOP 1

**EASTERN RESEARCH GROUP ATTENDEES**

Christopher Sese, Independent Assessor

**GENENTECH, INC. ATTENDEES**

Karen Jones, VP, Global Head Oncology Regulatory  
Cathi Ahearn, MBA Lifecycle Team Leader, Global Product Strategy Oncology  
O. Daejin Abidoye, MD, MPH Medical Director, Product Development Clinical Oncology  
Zachary Boyd, MS Sr. Companion Diagnostic Manager, Oncology Biomarker Development  
Vandana Chauhan, MS Regulatory Program Director, Pharma Technical Regulatory (PTR)  
Daniel S. Chen MD, PhD Cancer Immunotherapy Franchise Head, Product Development  
Clinical Oncology

David Chonzi, MD Safety Scientist Lead, Pharma Development Safety Risk Management

Joanna Chu, MS Program Manager, Product Development Regulatory

Graham Ross, MD, PhD Group Director, Product Development Clinical Oncology

Flavia Di Nucci, MD Senior Safety Scientist, Pharma Development Safety Risk Management

Jerald Grace, PharmD Associate Program Director, Product Development Regulatory

Kelly Gordon, PhD, MB (ASCPCM ) Companion Diagnostics Regulatory Affairs, Ventana Medical Systems

Benjamin Lyons, PhD Director, Biostatistics

Sarah Oliver, PhD US Principal Partner, Product Development Regulatory (PDR)

Melinda Teng, PhD Senior Statistical Scientist, Biostatistics

Mark Stroh, PhD Senior Scientist, Pharmacology Sub Team Leader & Clinical Pharmacology

Kathleen Winson, MS Group Director, Product Development Regulatory (PDR)

## 1.0 BACKGROUND

Genentech intends to submit a Biologics License Application (BLA) for atezolizumab (MPDL3280A) for use in patients with advanced urothelial bladder cancer (UBC). Recently, the proposed contents and format for this BLA have been discussed with the Agency and agreements have been reached for its submission. For this Type B meeting, the Sponsor aims to discuss and reach agreement on the acceptability of the results from two studies to support accelerated approval for the following proposed indication:

*“Atezolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma*

(b) (4)

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The two studies, including Cohort 2 of a phase 2 Study (GO29293) and the UBC cohort of a phase 1a study (PCD4989g), evaluated the activity and safety of atezolizumab in patients with locally advanced or metastatic UBC whose disease has progressed on or who were intolerant to a platinum-containing chemotherapy. In addition, the phase 2 study enrolled patients with untreated advanced UBC who were cisplatin-ineligible (Cohort 1). The key primary endpoint was objective response rate (ORR), as determined by Independent Review Facility (IRF). The overall ORR was further evaluated according to the PD-L1 IHC IC categories (IC0, IC1, and IC 2/3) of tumor specimens, which were assessed with Ventana’s anti-PD-L1 IHC Assay in a central laboratory. Based on the meeting package, the key efficacy results are summarized in the following table.

(b) (4)

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Key safety findings from patients with UBC are as follows. The most commonly reported adverse events ( $\geq 10\%$ ) included fatigue, decreased appetite, nausea, pyrexia, constipation, urinary tract infection, diarrhea, vomiting, dyspnea, and creatinine elevation. Immune-related adverse events (IMAEs) were observed in 26.0% of patients in Cohort 2 of the phase 2 study, including hepatic abnormalities, hyperthyroidism, colitis, pneumonitis, cytokine release syndrome, and rash. Approximately 5% of the IMAEs were assessed as grade 3 or 4. Note that a pooled safety analysis of IMAEs in approximately 2000 patients will be submitted according to the previous discussion and agreement between the sponsor and the review team.

Regarding Ventana's anti-PD-L1 IHC Assay, the sponsor has submitted two PMA modules to CDRH and plans to submit the last module concurrently with the proposed BLA submission.

FDA sent Preliminary Comments to Genentech, Inc. on September 16, 2015.

## **2. DISCUSSION**

### **Questions to the FDA**

#### **Question 1**

Does the Agency agree that the efficacy and safety results from the pivotal trial IMvigor 210 (GO29293) and supporting Study PCD4989g, as well as additional safety data from the NSCLC studies FIR (GO28625), POPLAR (GO28753) and BIRCH (GO28754) provide sufficient clinical evidence to characterize the benefits and risks of atezolizumab and to form the basis of a BLA for the identified patient population utilizing the accelerated approval pathway?

**FDA RESPONSE:** The results and data from the above clinical trials appear adequate to support the proposed BLA submission under Subpart E of the Biological Licensing Regulations.

We would like to obtain additional information on the duration of response in the phase 2 study (GO29293). You should use a data cutoff date in November 2015 for an updated analysis of the duration of response in this phase 2 study.

In your submission, please provide updated efficacy analyses of the UBC Cohort of the phase 1a study (PCD4989g) with a minimum follow-up time of 24 weeks (or 6 months). Your current proposed data cutoff date for this cohort was December 2, 2014, which was associated with a minimum follow-up time of 12 weeks according to the information in the meeting package. In addition, please clarify why in the same cohort, the number of patients with a PD-L1 IHC IC score of 2/3 (b) (4)

#### **GNE Response September 23, 2015**

The Sponsor acknowledges the Agency's request and would like to discuss with the Agency how to meet the Agency's requests without introducing a major delay to the filing submission date.

#### **Regarding the Agency's request for additional information on the duration of response in the phase 2 study (GO29293)**

We are preparing the primary analysis of Cohort 1 using a 14<sup>th</sup> September 2015 clinical cutoff, which will also include an update of Cohort 2 data.

As of this September data cutoff, all Cohort 2 patients would already have at least 42 weeks of follow-up. Our preliminary estimate for the September datacut would include the following:

(b) (4)



(b) (4)

The Sponsor proposes to include the updated results for all comers, IC 1/2/3, IC 2/3, IC1 and IC0 in cohort 2 on the following efficacy endpoints based on the September 2015 cutoff:

- ORR per IRF RECIST v1.1
- DOR per IRF RECIST v1.1

These updated results will be provided in the Summary of Clinical Efficacy (SCE) and summarized in the Clinical Overview (CO). As the CSR has now been finalized, the Sponsor proposes not to include the updated data in the IMvigor210 CSR, which is currently based on the final analysis for cohort 2. In addition, the Sponsor proposes that the updated IMvigor210 data will not be pooled with PCD4989g. The SDTM and derived datasets supporting the updated efficacy endpoints will also be submitted.

If the Agency is in agreement with the Sponsor's proposal, the Sponsor will assess the new submission date. At this time, we anticipate that this information could be included in the initial application without a significant delay.

Would the Sponsor's proposal to provide updated data from the 14<sup>th</sup> September 2015 data cutoff be adequate to meet the Agency's request?

**Regarding the Agency's request for updated efficacy analyses of the UBC cohort of the phase 1a study (PCD4989g) with a minimum follow-up time of 24 weeks (or 6 months)**

To meet the Agency's request for updated efficacy analysis for PCD4989g, Genentech proposes to provide efficacy data on ORR evaluable patients with at least 24 weeks of follow-up for the UBC cohort using the December 2014 cutoff. The Sponsor notes that as of the December 2014 data cut, (b) (4) have at least 24 weeks of follow-up.

The Sponsor proposes to include the following key efficacy analyses by IC status (IC 2/3, IC1, and IC0)) based on a minimum follow up time of 24-weeks:

- ORR per IRF-RECIST v1.1 (by IUO assay only)
- BOR per IRF-RECIST v1.1 (by IUO assay only)
- DOR per IRF-RECIST v1.1 (by IUO assay only)

The Sponsor proposes to include these additional analyses in the SCE and summarized in the CO as the PCD4989g CSR has now been finalized. As noted in our response to the request for for IMvigor210, the Sponsor proposes not to pool these updated data. The SDTM and derived datasets supporting the updated efficacy analysis will also be submitted.

Does the Agency agree with the Sponsor's proposal to provide updated specified efficacy analyses on the UBC cohort of PCD4989g, with at least 24 weeks of follow up, based on a December 2014 cutoff?

**Regarding the Agency's request for clarification on why the number of patients with a PD-L1 IHC IC score of 2/3** (b) (4)

The (b) (4) mUC patients with an IC score of 2/3 were assessed using the assay available at the time of enrollment on PCD4989g (primarily the prototype assay) in the April 2014 data cut. The IUO assay was used to retrospectively assess PD-L1 expression status among enrolled patients with evaluable tumor tissue. Based on cut-slide stability and evaluable tissue, a total of (b) (4) mUC patients had an IC score of 2/3 using the IUO assay in the December 2014 data cut.

Analyses using both the IOU and the assay available at the time of enrollment will be provided in the PCD4989g CSR. The PMA will only include analytical verification for the IUO assay.

*Meeting Discussion: The Sponsor plans to update the duration of response with a September cutoff. Additional data sweeps are up to the Sponsor. Submission of additional data concerning the duration of response during the review period is acceptable and would not be considered a major amendment. The Sponsor stated that the updated data concerning the duration of response will be in Module 2 in the Summary of Clinical Efficacy (SCE) and the Clinical Overview (CO).*

*The Sponsor plans to submit their BLA and datasets by the end of 2015, or early 2016. The datasets to support the updated information on the duration of response will be submitted 3 to 4 weeks after the initial BLA submission. The BLA submission would be considered complete when those datasets are submitted. The integrated safety datasets for most of the safety database will be submitted with the BLA, but a large NSCLC study (BIRCH), along with updated data from their large phase 1 study (PCD4989g), will be submitted in February 2016. This is acceptable. The Sponsor's proposal to use the evaluable patients in the UBC cohort of the phase 1 study is acceptable.*

**Question 2**

Based on the data from Study IMvigor 210 (GO29293) and supporting Study PCD4989g, the Sponsor proposes the following indication:

*Atezolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma* (b) (4)

[Redacted text block containing three lines of information, likely bulleted or numbered points, which have been obscured by grey bars.]

This indication statement will be supported by detailed description of the patient population in the Clinical Trials section of the label (see Section 12.1) for a description of the design of Study IMvigor210 [GO29293]). Can the Agency provide feedback into the acceptability of this indication?

**FDA RESPONSE: The detailed indication statement will be a review issue. In your submission of the Datasets and Clinical Study Report for Cohort 2 of GO29293, please include detailed information about patients who had evidence of disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen and [REDACTED] (b) (4). Provide analyses of IRF-assessed ORRs by each subset and by PD-L1 IC subgroup in each subset.**

**GNE Response September 23, 2015**

Genentech will provide IRF-assessed ORRs by IC status for the neoadjuvant or adjuvant subgroup in the initial filing documents.

We would like to clarify our original intention to pursue [REDACTED] (b) (4). After a more detailed review of the data, these patients cannot be clearly identified as a distinct population in cohort 2. Therefore we will not pursue this sub-group as part of our proposed labeled indication with this filing.

*Meeting Discussion: This appears to be acceptable. We may request additional data during the review process.*

**Question 3**

Based on the data presented from Study IMvigor 210 (GO29293) and supporting data from the Phase I Study (PCD4989g), does the Agency agree that atezolizumab [REDACTED] (b) (4) [REDACTED] ?

**FDA RESPONSE: This will be a review determination.**

[REDACTED] (b) (4)

**GNE Response September 23, 2015**

At this time, the Sponsor plans to complete the submission of a PMA for [REDACTED] (b) (4) diagnostic assay. The timeline is currently aligned with the BLA submission for atezolizumab in mUC. Based on the Agency's feedback on question 3, we acknowledge that the labeled population is a review issue.

In a situation for which the Agency would consider [REDACTED] (b)(4), we would like to discuss the role of [REDACTED] (b)(4) diagnostic assay at the Pre-BLA meeting.

***Meeting Discussion: The indicated population [REDACTED] (b)(4), will be a review issue. The diagnostic test could be considered [REDACTED] (b)(4) and a decision will be made during the review process. The Sponsor will continue with testing readiness activities.***

#### **Question 4**

Given recent discussions with the FDA and safety data provided to date, does the Agency agree that the proposed modified safety update would be acceptable in lieu of a 90-day post-BLA safety update?

**FDA RESPONSE: The proposal appears acceptable.**

#### **Question 5**

Does the Agency agree, given the unmet medical need for patients with metastatic urothelial carcinoma and the data presented from studies IMvigor 210 (GO29293) and PCD4989g, that these data demonstrate a substantial improvement over other available therapies, thus qualifying the proposed BLA for Priority Review?

**FDA RESPONSE: This will be determined at the time of our filing review. Given the Breakthrough Therapy designation for the intended indication, it is highly possible that this BLA would receive Priority Review if the submission is accepted.**

#### **Question 6**

Does the Agency agree that the data from Study IMvigor 210 (GO29293) would be adequate to support a Roche Tissue Diagnostics (VENTANA) PD-L1 (SP142) CDx Assay PMA submission [REDACTED] (b)(4)

**FDA RESPONSE: See Response to Question #3. In addition, this will depend on review findings from both the CDRH and CDER review divisions.**

**Question 7**

The Sponsor is currently conducting a pivotal Phase III Study IMvigor 211 (GO29294), evaluating the safety and efficacy of atezolizumab compared with chemotherapy (taxanes or vinflunine) in patients with metastatic urothelial carcinoma. Does the Agency agree that the current study design is acceptable for conversion from accelerated to full approval for patients with locally advanced or metastatic urothelial carcinoma [REDACTED] (b) (4) [REDACTED] (ie, Cohort 2 of Study IMvigor 210 [GO29293])?

**FDA RESPONSE: Evidence required for the product to receive regular approval for the intended indication will depend on both trial results and conduct. As discussed previously, the trial design for this randomized study is acceptable.**

**Question 8**

Does the Agency agree with the submission plan and submission date for Module 3 (Chemistry, Manufacturing and Controls) and Module 4 (Nonclinical) currently planned for October 2015?

**FDA RESPONSE: The plan is acceptable.**

**Question 9**

Does the Agency foresee that the proposed BLA will be reviewed by the Oncologic Drugs Advisory Committee (ODAC)?

**FDA RESPONSE: If potential ODAC issues are identified during our review, you will be notified.**

**Question 10**

Would the Agency like to have an orientation meeting with the Sponsor after the submission of the BLA to outline the major components of the BLA?

**FDA RESPONSE: Yes. We expect that you will present your findings after all modules are submitted.**

**3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. The content of the application was outlined in Question #1.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that whether or not a REMS will be needed will be based on the review findings of the BLA.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: The datasets to support the updated information on the duration of response will be submitted 3 to 4 weeks after the initial BLA submission. The BLA submission would be considered complete when those datasets are submitted.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

**BLA NUMBER: LATE COMPONENT - BIOMETRICS**  
**BLA NUMBER: LATE COMPONENT - CLINICAL**  
**BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY**  
**BLA NUMBER: LATE COMPONENT - NONCLINICAL**  
**BLA NUMBER: LATE COMPONENT - QUALITY**

In addition, we note that a multidiscipline pre-submission meeting was held on October 8, 2014. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

### **PREA REQUIREMENTS**

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

*Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## **Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is

intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

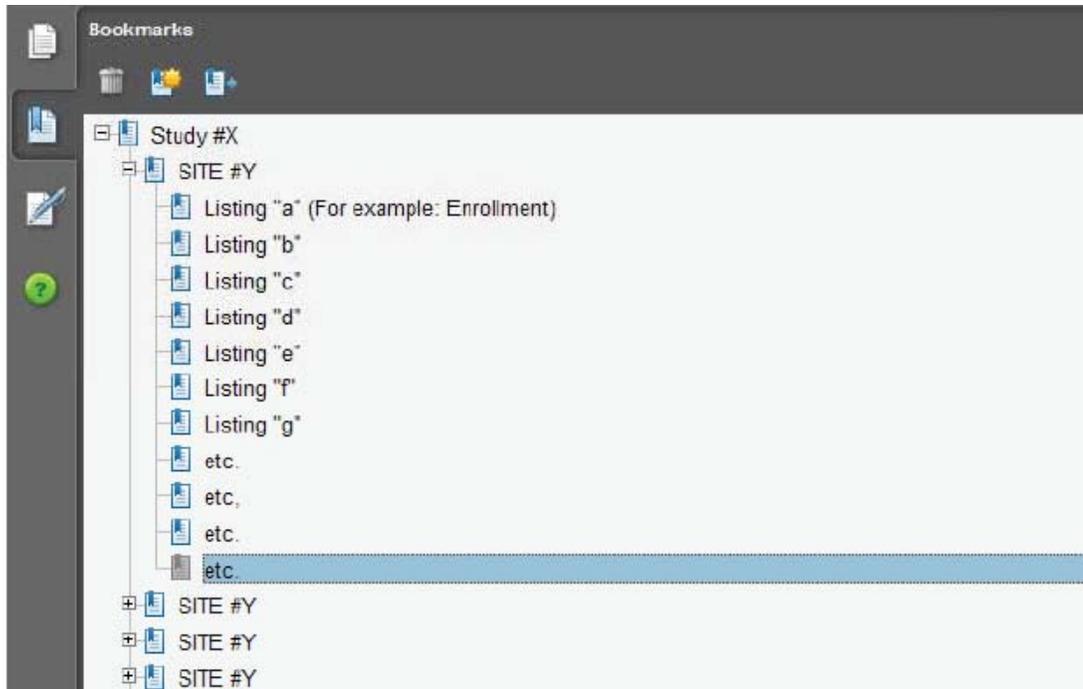
**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
  
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
  
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

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

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

## Attachment 1

### Technical Instructions:

#### Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page  
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

N/A

**5.0 ACTION ITEMS**

N/A

**6.0 ATTACHMENTS AND HANDOUTS**

N/A

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/s/  
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VIRGINIA E MAHER  
10/24/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

IND 120827

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Jerald Grace, PharmD.  
Regulatory Program Management

Dear Dr. Grace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Atezolizumab, 60 mg/mL.

We also refer to your correspondence, dated and received March 20, 2015, requesting review of your proposed proprietary name, Tecentriq.

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

A request for proprietary name review for Tecentriq should be submitted once the BLA is submitted.

If any of the proposed product characteristics as stated in your March 20, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Kim Robertson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, 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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TODD D BRIDGES  
06/20/2015



IND 120827

## MEETING MINUTES

Genentech, Inc.  
Attention: Jerald Grace, Pharm. D.  
Associate Program Director, Product Development, Regulatory  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Grace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MPDL3280A.

We also refer to the teleconference between representatives of your firm and the FDA on May 11, 2015. The purpose of the meeting was to reach agreement on the proposed content and format of the BLA to support the proposed indication and enable accelerated approval, to gain feedback on the overall approach to the BLA filing, and on the content and format of the clinical, clinical pharmacology, nonclinical pharmacology, toxicology, and statistical sections of the application.

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

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

V. Ellen Maher, MD  
Clinical Team Leader  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** May 11, 2015; 12Noon, EST  
**Meeting Location:** Bldg. 22; Conf. Room 4201

**Application Number:** 120827  
**Product Name:** MPDL3280A  
**Indication:** Urothelial Bladder Cancer (UBC)  
**Sponsor/Applicant Name:** Genentech, Inc.

**Meeting Chair:** V. Ellen Maher, M.D.  
**Meeting Recorder:** Kim J. Robertson

**FDA ATTENDEES**

Geoffrey S. Kim, M.D., Director, DOP1  
V. Ellen Maher, M.D., Clinical Team Leader, DOP1  
Yang-Min (Max) Ning, M.D., Ph.D., Clinical Reviewer, DOP1  
Todd Palmby, Ph.D., Non-Clinical Team Leader, DHOT  
Shenghui Tang, Ph.D., Biometrics Team Leader, DBV  
Erik Bloomquist, Ph.D., Biometrics Reviewer, DBV  
Joel Welch, Ph.D., CMC, Lead Chemist, OBP  
Xianghong (Emily) Jing, Ph.D., Chemistry Reviewer, OBP  
Kim J. Robertson, Regulatory Health Project Manager, DOP1

**GENENTECH, INC. ATTENDEES**

Cathi Ahearn, MBA, Lifecycle Team Leader, Global Product Strategy Oncology  
Daejin Abidoye, M.D., MPH, Medical Director, Product Development Clinical Oncology  
Vandana Chauhan, M.S., Regulatory Program Director, Pharma Technical Regulatory (PTR)  
James T. Cross, Ph.D., Program Director, Product Development Regulatory (PDR)  
Gregg Fine, MD, Medical Director, Product Development Clinical Oncology  
Jerald Grace, Pharm.D., Associate Program Director, Product Development Regulatory (PDR)  
Benjamin Lyons, Ph.D., Associate Director, Biostatistics  
Howard Mackey, PhD, Principal Statistical Scientist, Biostatistics  
Chris McKenna, Manager, Statistical Programming and Analysis  
Nathan McKnight, Ph.D., Technical Development Lead, Pharma Technical Development  
Hina Patel, Pharm.D., Senior Safety Scientist, Pharma Development Safety Risk Management

**GENENTECH, INC. ATTENDEES (cont.)**

Rodney Prell, Ph.D., Senior Scientist/Toxicologist, Safety Assessment and Toxicology

Mark Stroh, Ph.D., Senior Scientist, Clinical Pharmacology

Kathleen Winson, M.S., Group Director, Product Development Regulatory (PDR)

**1.0 BACKGROUND**

MPDL3280A is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits its interactions with PD-1 and B7.1. The antitumor activity of MPDL3280A has been demonstrated in a number of malignancies, including advanced urothelial bladder cancer (UBC).

Based on the preliminary clinical findings from the UBC cohort of a phase 1a study (PCD4989g), MPDL3280A received Breakthrough Therapy designation in 2014 for the treatment of patients with locally advanced or metastatic UBC that is PD-L1 positive, as (b) (4), after progression on or intolerance to a platinum-containing chemotherapy. To attain adequate evidence for this intended indication, a phase 2 trial (GO29293) is being conducted in 438 patients with advanced UBC and the primary endpoint is objective response rate, as assessed with RECIST v1.1 per Independent Review. The estimated data availability time is July-December of 2015. With the Agency's feedback and previous discussions between DOP1 and the Sponsor, results from this phase 2 study along with those from the phase 1a UBC cohort (N=103) will be included in the BLA submission. This may support accelerated approval.

For this Type B meeting, the Sponsor seeks feedback from the Agency and would like to reach agreement on the content and format of the planned BLA submission. Note that MPDL3280A is not commercially available in any countries at this time.

As part of the development plan in UBC and to provide evidence for conversion from accelerated approval to full approval, the Sponsor is also conducting a randomized, active-controlled, open-label phase 3 trial in patients with locally advanced or metastatic UBC that have progressed during or following a platinum-containing regimen (GO29294). The primary endpoint is overall survival. Results from this study will not be available until 2017.

FDA sent Preliminary Comments to Genentech, Inc. on May 8, 2015.

**2. DISCUSSION**

**Question 1:**

Does the Agency agree with the proposed plan for submitting the CSRs for the pivotal study GO29293 and supporting Phase Ia study PCD4989g, as described in Section 15.2?

**FDA Response:**

**Safety analyses should have a data cutoff date no greater than 6 months prior to submission of a BLA.**

**Given the two different cohorts in Study GO29293, safety and efficacy analyses should be reported for each cohort in the CSR.**

**Genentech's Response May 11, 2015:**

Could the Agency please clarify that scope of the 6 month data cutoff date refers to both GO29293 as well as PCD4989g?

Including additional safety data beyond that which is currently being proposed would most likely result in a delay to the submission. The extent of the delay would be dependent in part on the scope of pooling as noted in question #7.

We acknowledge the Agency's response to question #12 regarding the possibility to waive the 90 day safety update. Genentech would like to propose a modified safety update that would take into consideration the importance of providing this additional safety data as close to the original BLA submission as possible. Would the Agency be amenable to considering this alternate strategy?

In reference to your last comment above, Genentech plans to conduct separate safety and efficacy analyses by cohort in the GO29293 CSR as specified in the SAP.

***Meeting Discussion: The Sponsor will provide a detailed proposal on the safety data, that will be included in the original BLA and the safety data that will be included in a modified safety update. This proposal will be submitted with a request for a Type A meeting.***

**Question 2:**

Does the Agency agree with the proposed plan for submitting narratives for the pivotal Study GO29293 and supporting Study PCD4989g, as described in Section 15.3.4.2?

**FDA Response:**

**In addition to the listed criteria for submission of narratives, you should include narratives for the following patients:**

- **Patients who experienced an immune-mediated adverse event requiring systemic corticosteroids. This should include information on the duration of corticosteroid dosing and data on the outcome of the event.**
- **Patients who experienced an SAE that was considered related to study treatment by the investigators.**
- **Patients who discontinued study treatment due to reasons other than disease progression or death.**
- **Patients who died within 30 days after the last dose of study treatment and whose death was attributed to an adverse event or disease progression by the investigator.**

**Additional narratives should be available upon request during review. For example, a narrative from a patient who experienced an SAE (e.g., serious pneumonitis) that was considered as unrelated to study treatment by the investigator, but is found important to our clinical review.**

**Genentech's Response May 11, 2015**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 3:**

Does the Agency agree with the proposed submission of eCRFs for the pivotal Study GO29293 and supporting Study PCD4989g, as described in Section 15.3.5?

**FDA Response:**

**CRFs should be submitted for all patients whose narratives are required as listed in response to Question 2.**

**Additional CRFs should be available upon request.**

**Please index your submitted CRFs with study patient unique ID number.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 4:**

Does the Agency agree with the plan not to provide radiographic images in the BLA, but to make these images available on request for the pivotal Study GO29293 and supporting Study PCD4989g UBC cohort, as described in Section 15.3.6?

**FDA Response:**

**Submission of radiographic images is not required.**

**Please submit datasets from the Independent Review Committee for Studies GO29293 and PCD4989g.**

**GNE Response May 11, 2015**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 5:**

Does the Agency agree with the proposed statistical analysis plans for studies GO29293 and PCD4989g, as presented in Appendix 8 and Appendix 9?

**FDA Response:**

**Yes. In general, your proposed statistical analysis plans appear acceptable.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 6:**

Does the Agency agree with the proposal to use a 30-day window for AE summaries (except for treatment related SAEs) for studies GO29293 and PCD4989g, as described in Section 14.1.2 and Section 14.2.2, and in the proposed statistical analysis plans for these studies (Appendix 8 and Appendix 9)?

**FDA Response:**

**We agree that in the proposed safety analyses, you should include adverse events that occur within 30 days after the last dose of study treatment or before the initiation of new anti-cancer therapy.**

**Immune-mediated adverse events (both serious and non-serious) should be submitted regardless of the 30-day window.**

**Patients with SAEs or laboratory abnormalities that occurred during the same time window, regardless of causality assessment, should also be included in the safety analyses.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments.

With regard to the feedback on SAEs or laboratory abnormalities, could the Agency please clarify what is meant by "during the same time window"?

*Meeting Discussion: SAEs and laboratory abnormalities that occur within 30 days of the last dose of study treatment should be included in the safety analyses.*

***\*Comments Added after the Meeting: Immune-mediated serious adverse events that occur more than 30 days after the last dose of study drug should be included in both the safety datasets and narratives of a BLA submission.***

**Question 7:**

Does the Agency agree with the proposed statistical analysis plans for the integrated and pooled safety analysis across PCD4989g (UBC cohort) and GO29293 in the ISS and SCS, as described in Section 15.5?

**FDA Response:**

**We agree with your proposal to conduct pooled safety analyses for patients with UBC from the two studies.**

**We are concerned that the safety database you propose will provide limited information concerning uncommon adverse events. You should conduct additional pooled safety analyses in all patients who received MPDL3280A monotherapy on Studies PCD4989g, GO29293, GO28625, GO28753, and GO28754.**

**Genentech's Response May 11, 2015:**

Regarding your request for additional pooled safety analysis, Genentech would like to clarify the following:

1. Is it the Agency's expectation that all tumor-types will be included in the pooled analysis for PCD4989g?

*Meeting Discussion: Yes.*

2. Is it the Agency's expectation that the data cutoff from the NSCLC studies fall within 6 months of the UBC BLA submission as noted in question #1?

[Redacted] (b) (4)

Therefore, would the Agency be open to Genentech submitting an alternate proposal to address the request for additional monotherapy safety data? [Redacted] (b) (4)

[Redacted]

As noted in Genentech's response to question #1, the proposal would take into consideration the importance of providing the updated information as close to the original BLA submission as possible.

*Meeting Discussion: The Sponsor proposed various cutoff dates for the lung studies that will be included in the pooled safety analysis.* [Redacted] (b) (4)

[Redacted]

**Question 8:**

Does the Agency agree with the proposed statistical analysis plans for the integrated and pooled efficacy analysis across PCD4989g (UBC cohort) and GO29293 in the ISE and SCE, as described in Section 15.4?

**FDA Response:**

**As the meeting package indicates that the proposed efficacy analyses are considered exploratory, the Agency has no objection to the proposed analyses.**

**Genentech's Response May 11, 2015**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 9:**

Does the Agency agree with the proposed content of the Module 5 datasets package submission, including the structure and format of the datasets for the pivotal Study GO29293 and supporting study PCD4989g, as described in Section 15.3.7?

**FDA Response:**

**Please see response to Question 7. Datasets should be provided to support the pooled safety analyses.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments. Please see Genentech's response to Question 7.

*Meeting Discussion: No further discussions were necessary.*

**Question 10:**

Does the Agency agree with Genentech's plans for the collection and organization of supporting documentation for the overall Table of Contents of the BLA, as described in Appendix 10?

**FDA Response:**

**Yes; your plans are acceptable.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 11:**

Does the Agency agree with Genentech's proposal to not include a Risk Evaluation and Mitigation Strategy (REMS) for the use of MPDL3280A in UBC, as described in Section 15.3.4.1?

**FDA Response:**

**Whether a REMS will be needed will be based on review findings from the BLA.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 12:**

Does the Agency agree with Genentech's proposal for a 90 day Safety Update, as described in Section 15.5.11?

**FDA Response:**

**Your proposal concerning a 90-day Safety Update appears acceptable. Depending on the results from Study GO29293, this update may be waived to expedite early patient access to the product. We will examine this issue at the time of filing of the BLA.**

**Genentech's Response May 11, 2015:**

We acknowledge the Agency's response regarding the possibility to waive the 90 day safety update.

Please see Genentech's response to Questions 1 and 7.

*Meeting Discussion: No further discussions were necessary.*

**Question 13:**

On the basis of existing data, are the planned content and format of clinical pharmacology and biopharmaceutics data in support of the BLA acceptable to the Agency, as described in Section 15.6?

**FDA Response:**

**Your proposal is acceptable.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments.

*Meeting Discussion: No further discussions were necessary.*

**Question 14:**

On the basis of existing data, are the planned content and format of the non-clinical pharmacology and toxicology data in support of the BLA acceptable to the Agency, as described in Section 15.7?

**FDA Response:**

**No. The longest duration completed repeat-dose toxicology study described in your meeting briefing package is an 8-week IV study in Cynomolgus monkeys, although ICH S9 recommends 3-month studies to support phase 3 clinical trials for a marketing application. In your BLA submission, provide an interim report from the ongoing 26-week repeat-dose IV toxicology study in Cynomolgus monkeys described in your meeting briefing package. Provide as much data from this study as possible, depending on what phase this study is in when you submit your BLA (e.g., in-life data or complete data from animals at the end of dosing). In addition, indicate whether toxicokinetic data from the 8-week repeat-dose IV toxicology study in Cynomolgus monkeys demonstrate continued exposure to MPDL3280A in recovery animals for a period of time following the last dose, which may provide additional data in animals exposed for longer than 8 weeks. Together, these data may be sufficient to support a BLA submission.**

**If the final study report from the 26-week repeat-dose toxicology study becomes available following the BLA submission but during our review, you may submit that report to your BLA at that time. If the final study report for the 26-week toxicology study is not available during our review of your BLA, a post-marketing requirement may be needed.**

**In addition to the pharmacology studies described in the meeting briefing package, please include any data characterizing the potential effects on immune recall or memory responses, if available.**

**The content of your proposed nonclinical data described in your meeting briefing package, other than those discussed above, appear sufficient to support a BLA submission. The adequacy of the submitted nonclinical data to support approval of a BLA will be determined following our review of your BLA submission.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments regarding the 26-week repeat-dose toxicology study report. An audited draft report will be available at the time of Module 4 submission (planned for October 2015). Genentech will provide a final study report as part of the BLA filing once available. If the final report is not available at the time of the filing, the final study report will be provided during BLA review.

Data from the 8-week repeat-dose toxicology study has demonstrated maintained exposures for up to 20 weeks and will be provided in the BLA.

Data characterizing MPDL3280A's potential effects on immune recall or memory responses will not be available at the time of BLA submission, [REDACTED] (b) (4)

Genentech would like to clarify that a developmental and reproductive toxicology study is not planned for this BLA submission.

***Meeting Discussion: The Sponsor's proposal appears acceptable. The Agency also agrees that a developmental and reproductive toxicology study is not needed to support the BLA submission.***

**Question 15:**

Does the Agency agree with Genentech's plan for rolling submission, as described in Section 15.9?

**FDA Response:**

**Yes.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's comments.

***Meeting Discussion: No further discussions were necessary.***

**Additional Comments:**

- 1. Specify when your PMA for PD-L1 assay in UBC will be submitted relative to the planned BLA submission.**

**Genentech's Response May 11, 2015:**

The final module of the PMA (clinical module) will be submitted at the same time as the BLA. The four modules will be filed on these dates:

- Module 1: Software and Hardware, June, 2015
- Module 2: Quality and Manufacturing, July, 2015
- Module 3: Non-clinical (Analytical) Studies, November, 2015
- Final Module: Clinical Studies, January, 2016

***Meeting Discussion: No further discussions were necessary.***

- 2. Provide items requested by the Office of Scientific Investigations (OSI) prior to or in your BLA submission. These items are listed in Section 3 of the meeting minutes.**

**Genentech's Response May 11, 2015:**

Genentech acknowledges the Agency's request. No further comments.

***Meeting Discussion: No further discussions were necessary.***

- 3. Please explain why an interim analysis will be presented for Cohort 1 of GO29293 in the proposed BLA. It is our understanding that this cohort has completed enrollment and that Module 5 will be submitted in January 2016.**

**Genentech's Response May 11, 2015:**

Although all patients in Cohort 1 will have completed their 6-month follow-up in Q4 2015, only top-line data from the final analysis will be available by December 2015. Therefore, the only data that is currently planned to be included in the BLA in January 2016, will be the results of the interim analysis.

*Meeting Discussion: The Sponsor's final analysis will not be performed until all patients have completed 6 months of therapy. Therefore, the final analysis will be conducted using data with an October 2015 cutoff. The Sponsor expects that the final analysis, including datasets, will be available two to three months after the BLA submission.*

- 4. Please comment on the enrollment of GO29294 at the time of submission of the proposed BLA.**

**Genentech's Response May 11, 2015:**

At the time of the proposed BLA submission (January 2016), approximately 500 patients (out of the 767 total planned) will be enrolled in study GO29294.

*Meeting Discussion: No further discussions were necessary.*

### **3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

The content of a complete application was discussed. Agreements were not reached during this meeting. The Sponsor will provide a detailed proposal on the safety data, that will be included in the original BLA and the safety data that will be included in a modified safety update. This proposal will be submitted with a request for a Type A meeting.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held and it was concluded that whether or not a REMS will be needed will be based on the review findings of the BLA.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a multidisciplinary pre-submission meeting dated October 8, 2014, and a chemistry only meeting dated March 11, 2015, were held. We refer you to the minutes of those meetings for any additional agreements that may have been reached.

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

N/A

**5.0 ACTION ITEMS**

N/A

**6.0 ATTACHMENTS AND HANDOUTS**

N/A

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/s/  
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VIRGINIA E MAHER  
05/22/2015



IND 120827

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Genentech, Inc.  
Attention: Jerald Grace, Pharm.D.  
Associate Program Director, Product Development Regulatory  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Grace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MPDL3280A.

We also refer to your March 24, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that MPDL3280A for the treatment of patients with locally advanced or metastatic urothelial bladder cancer that is PD-L1 positive, (b) (4) after progression on or intolerance to a platinum-containing chemotherapy regimen meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of MPDL3280A for urothelial bladder cancer to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Attachment 1 lists potential topics for discussion at this initial breakthrough therapy meeting. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*<sup>2</sup> for procedures on requesting a meeting. If you feel that submitting a meeting request

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for MPDL3280A for urothelial bladder cancer is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

Amna Ibrahim, M.D.  
Acting Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

**Attachments:**

Attachment 1: Breakthrough Designated Product, Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor, Potential Topics for Discussion

**Attachment 1: Breakthrough Designated Product**  
**Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor**  
**Potential Topics for Discussion**

**General/Regulatory:**

- Planned target date for NDA/BLA submission, including plans for rolling review
- Other indications in development
- Expanded access plans, including intent to communicate these plans publicly
- Plans to seek accelerated approval
- Regulatory status with non-U.S. regulatory agencies
- Plans to defer or waive studies or trials, including those to be conducted as postmarketing commitments/postmarketing requirements (PMC/PMRs)
- Rationale for proposed flexibility in study and trial design
- Plans for submission of a proprietary name request
- If a drug/device combination product, device development information and plan
- In-vitro diagnostic development plan with the Center for Device and Radiologic Health (CDRH)
- Target product profile for proposed indication
- Gantt chart of development timeline, including information on all areas noted below
- Proposed communication plan for periodic development program updates to the FDA, including timelines and content

**Clinical Activity and Data Analysis:**

- Existing and planned clinical sites and accrual data
- Efficacy
  - Status of all clinical studies and topline summary results
  - Preliminary evidence of proof of concept
  - Planned or completed clinical trials intended to support efficacy, including:
    - Overall study design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials, Type I error control, and expected initiation/completion dates
    - Validity of the outcomes and endpoints. If using drug development tools, such as a patient reported outcomes or biomarkers, plans for the development and validation of the instrument, if appropriate.
- Safety
  - Potential safety issues from nonclinical studies/early clinical trials
  - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, and immunogenicity safety profile
  - Clinical trials safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for post-market drug safety and surveillance (pharmacovigilance)
    - Proposed size of safety population
    - Plan or need for long-term safety studies

- Pre-approval
- Post-approval
- Plans to mitigate/minimize risk, proposed Risk Evaluation and Mitigation Strategy (REMS)
- Specific Populations
  - Dose, study design, efficacy endpoints, size and composition of population, additional safety trials, for populations such as:
    - Geriatrics
    - Pediatrics
    - Hepatically/Renally Impaired
  - Proposed pediatric development plan with outlines/synopses of additional studies.

### **Clinical Pharmacology and Pharmacokinetics:**

- Justification for all dose selections, including number of doses, dose intervals, etc
- Clinical pharmacology, pharmacodynamics, and pharmacokinetics studies: completed, ongoing, planned, and requests for deferral, such as:
- Immunogenicity
- Dosing
  - Single ascending dose
  - Multiple ascending dose
  - Dose response study
- Food-effect
- Drug-drug interactions (DDI)
- Thorough QT/QTc
- Organ impairment
- Pharmacogenomics
- Plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
- Plans for conducting population pharmacokinetics, exposure-response modeling/simulation analyses
- Plans to describe dose modifications in labeling based on DDI, age, organ impairment, etc.
- 

### **Nonclinical Pharmacology, Pharmacokinetics, and Toxicology**

- Nonclinical studies completed, ongoing, and planned, including, the number and sex of animals per dose, doses, route of administration, toxicities, duration of study and study results. For studies planned timelines for initiation and submission of study reports. Examples of such studies include:
  - Subacute and chronic toxicology
  - Gene toxicology
  - Reproductive toxicology
  - Carcinogenicity studies
  - Animal models of disease and PK parameters associated with efficacy

- Evidence of mechanism of action
- Safety pharmacology, where appropriate
- Disease specific animal models

**Chemistry, Manufacturing, and Controls:**

- Drug product:
  - Dosage form
  - Formulation description
  - Administration instructions, delivery systems (e.g. vials, pre-filled syringes, etc.) proposed draft packaging, and disposal instructions
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life and required stability studies
- Drug substance:
  - Characterization
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life or retest period and required stability studies
- Proposed commercial processes:
  - Manufacturing process, in process controls, scale-up plans
  - Comparison of proposed commercial manufacturing processes to clinical manufacturing processes
  - Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability
  - Current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
  - Current release and stability testing site(s) and proposed commercial testing site(s), if different
  - Anticipated market demand at launch
- Proposed validation approaches:
  - Drug substance and drug product manufacturing process
  - Microbial control and sterility assurance
  - Viral clearance
  - Analytical methods

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/s/  
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AMNA IBRAHIM  
05/22/2014

## Clinical Evaluation of the Breakthrough Therapy Designation Request for MPDL3280A

### Summary Box

1. **IND Number:** 120827
2. **Company name:** F. Hoffmann-La Roche Ltd
3. **Drug name:** MPDL3280A
4. **Intended Indication:** for the treatment of patients with locally advanced or metastatic urothelial bladder cancer (UBC) that is PD-L1 positive, (b) (4) after failure of a platinum-containing chemotherapy regimen
5. **Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition?** Yes, used alone
6. **Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints?** Yes
7. **CDER Medical Policy Council Assessment:** Concurred with the recommendation. The final decision was communicated to the review team on May 14, 2014 (see Appendix).

**Division:** Office of Hematology and Oncology Products DOP1

**Medical officer:** Y Max Ning, MD, PhD

**Clinical Team Leader:** V Ellen Maher, MD

### 1. Brief description of the drug

MPDL3280A is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits interaction with its receptors including programmed cell death 1 (PD-1) and B7-1. The inhibition is expected to enhance tumor-specific T-cell responses, resulting in improved anti-tumor immune responses. Preliminary clinical evidence showed that its antitumor activity appears to be higher in PD-L1 positive tumors.

### 2. Brief description of the disease and intended population

Bladder cancer is the fifth most common cancer in the United States with an estimated 73,510 new cases in 2012 according to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) statistics. Approximately 14,880 deaths from advanced bladder cancer are anticipated in 2012. For locally advanced (inoperable) and metastatic urothelial bladder cancer (UBC), platinum-based chemotherapy such as GC (gemcitabine and cisplatin) or MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) is commonly used as first-line therapy. However, almost all patients experience disease progression or are intolerant to treatment. There is no standard second-line therapy (See Section 4). The reported median survival of patients after platinum-based therapy is about 6-11 months, with a median progression-free survival of only 3-4 months in the second-line setting.

The intended study population for this Breakthrough Therapy Designation request targets patients with locally advanced or metastatic urothelial bladder cancer after progression during or following treatment

with a platinum-containing chemotherapy regimen. Clearly, this represents a life-threatening disease because of the dismal survival.

### **3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area**

The sponsor intends to use the objective response rate and duration of response in an ongoing Phase 1 cohort of patients whose tumor specimens test positive for PD-L1. A positive test is defined as an immunohistochemistry (IHC) score of 2 or 3 with Ventana's anti-PD-L1 IHC Assay (b) (4).

The sponsor is planning a single-arm, open label Phase 2 trial to further assess independently reviewed response rates in the intended patients regardless of PD-L1 IHC status [either positive (IHC 2/3) or negative (IHC 0/1) based on test results from a central laboratory]. The primary endpoint will be the response rate in patient's whose tumor samples test positive for PD-L1. This trial also plans to enroll 30 patients ineligible (unfit) for cisplatin-based therapy. Results from this trial are intended for accelerated approval of MPDL3280A (b) (4) population of patients with UBC whose disease has progressed after a platinum-containing regimen. Response rate, in second-line therapy for this disease is a reasonable endpoint for accelerated approval.

The sponsor is also planning to conduct a randomized, active-controlled, open-label Phase 3 trial of MPDL3280A in patients with locally advanced or metastatic UBC with overall survival as the primary endpoint. Patients eligible for this trial must have disease progression during or following a platinum-based regimen, and the proposed active control is investigator's choice (b) (4). This trial is intended for conversion of MPDL3280A to full approval if this drug receives accelerated approval.

Given the limited objective responses observed with products or regimens used in the second-line setting, a high, confirmed objective response rate along with sustained response duration is considered reasonably likely to predict clinical benefit in patients receiving MPDL3280A. This endpoint would support accelerated approval (b) (4). The use of overall survival in the planned active-controlled Phase 3 trial may be able to establish or verify the clinical benefit of MPDL3280A in the intended patient population.

### **4. Brief description of available therapies (if any)**

There is no FDA-approved product or standard therapy for UBC in the second-line setting. Outside the USA, vinflunine is approved as second-line therapy. Therapies studied or used in patients with advanced UBC after platinum-based chemotherapies are summarized in the following table.

	Vinflunine <sup>1</sup> +BSC	Gemcitabine + Paclitaxel <sup>2</sup>	Docetaxel <sup>3</sup>	Nab-paclitaxel <sup>4</sup>
Trial Phase	III	III	II	II
<b>Objective Response (#Evaluable Patients)</b>	<b>N = 185</b>	<b>N = 40</b>	<b>N = 70</b>	<b>N = 47</b>
Overall RR	16 (9%)	15 (38%)	5 (11%)	13 (28%)
Response Duration (mos), median	7.4	NR	NR	NR
<i>NR not reported;</i> 1. BeBellmunt J. et al. (2009) <i>J Clin Oncol</i> 27 4454-4461. An improvement in OS (not statistically significant) was seen. 2. Albers P et al. (2011) <i>Annals of Oncology</i> 22 288-294. 3. Choueiri TK et al (2011) <i>J Clin Oncol</i> 30 507-512. 4. Ko YJ et al (2013) <i>Lancet Oncol</i> 2013; 14 769-76.				

**5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation**

None in the intended disease setting

**6. Description of preliminary clinical evidence**

The sponsor submitted preliminary evidence from 20 patients with locally advanced or metastatic UBC with a PD-L1 IHC score of 2 or 3 who were enrolled in an MPDL3280A expansion cohort (15 mg/kg, q 3 weeks) of an ongoing single-arm Phase 1a study (PCD4989g). Key baseline characteristics of the 20 patients are: all had an ECOG performance score of 0-1, with a median age of 69 years; 13 (65%) had visceral metastases; and 19 (95%) received prior platinum-based chemotherapy. Regarding the time interval from last platinum treatment to study entry (TIPS), 7 patients with metastatic disease had an interval of <12 months (3.0 -8.0), and 12 with metastatic disease or locally advanced disease had an interval of >12 months (13.0 -22.0).

The response and current treatment status are shown in the following figure. The median treatment duration as of the data cutoff was 4.5 months. The median follow-up duration was 5.4 months (1.8-3.3+), with 10 responding patients still on MPDL3280A.



Confirmed objective response (per RECIST v1.1) rate was 50%. The median response duration was not reached (observed range: 2.9-7.5 months) as of the data cutoff of Jan. 1, 2014. In the 19 patients with prior platinum therapy, the response rate was 47%.

Four of the 7 patients with a TIPS interval of 3-8 months had confirmed responses (a rate of 57%), and 5 of the 12 patients with a TIPS interval of 13-22 months responded (a rate of 42%). This may suggest that treatment effect of MPDL3280A was not necessarily associated with when prior platinum therapy was administered.

In updated data, the sponsor provided information from all evaluable patients with PD-L1 IHC 2/3 UBC (N=30) or with PD-L1 IHC 0/1 UBC (N=35). This includes confirmed and unconfirmed responses as shown in the following figures.

**IHC 2/3: (N=30)**

**IHC 0/1: (N=35)**



The ORR (confirmed and unconfirmed response) in the PD-L1 IHC 2/3 cohort was 43.3% and included 2 patients (6.7%) with complete response. In contrast, the ORR (confirmed and unconfirmed response) in the PD-L1 IHC 0/1 cohort was 11.4%. The difference between the two cohorts in objective responses appears considerable, suggesting that patients with IHC 2/3 UBC may respond to MPDL3280A better.

**7. Division's recommendation and rationale**

- The Division recommends that the Breakthrough Therapy Designation request for MPDL3280A for the proposed indication be granted.
- Rationales:
  - Locally advanced or metastatic UBC after failure of a platinum-containing chemotherapy regimen is a serious and life-threatening disease.
  - The preliminary evidence for MPDL3280A in patients with advanced UBC who have received a prior platinum-based regimen and whose tumors are PD-L1 positive shows a considerably higher response rate (47%) than the reported with other products used as

second-line therapy. Median response duration has not been reached with an overall median follow-up time of 5.4 months.

**8. Division's next steps and sponsor's plan for future development**

The division has completed the review of the Phase 2 trial protocol and has sought input from the CDRH team regarding the (b) (4) diagnostic. A meeting has also been scheduled with the sponsor in the next month to discuss its development plan.

**Appendix: Key Emails Related to the Clinical Assessment of the BT Designation Request**

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**From:** Benton, Sandra J  
**Sent:** Wednesday, May 14, 2014 7:46 AM  
**To:** Woodcock, Janet; Ning, Yang-Min (Max); Temple, Robert; Jenkins, John K; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B; Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Robertson, Kim; Maher, Virginia E.; Ibrahim, Amna  
**Subject:** RE: May 16, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 120827

As the Council agrees with DOP1's recommendation to grant F. Hoffmann-La Roche's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the May 16, 2014 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton

Senior Policy Analyst

CDER/Office of Medical Policy

301-796-1042 [sandra.benton@fda.hhs.gov](mailto:sandra.benton@fda.hhs.gov)

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**From:** Woodcock, Janet  
**Sent:** Friday, May 09, 2014 8:42 AM  
**To:** Ning, Yang-Min (Max); Benton, Sandra J; Temple, Robert; Jenkins, John K; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B; Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Robertson, Kim; Maher, Virginia E.; Ibrahim, Amna  
**Subject:** RE: May 16, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 120827

Thanks. That was what I was focusing on. (b) (4), (b) (5)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Jw

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**From:** Ning, Yang-Min (Max)  
**Sent:** Thursday, May 08, 2014 10:55 PM  
**To:** Woodcock, Janet; Benton, Sandra J; Temple, Robert; Jenkins, John K; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B; Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J;

Pazdur, Richard; Rosebraugh, Curtis; Robertson, Kim; Maher, Virginia E.; Ibrahim, Amna

**Subject:** RE: May 16, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 120827

Dr. Woodcock,

We have already scheduled a meeting with the sponsor next month to discuss the proposed development plan: 1) to conduct a large Phase 2 trial to verify or further assess independently reviewed response rates in patients with advanced UBC that tests positive (IHC 2/3) or negative (IHC 0/1) for PD-L1; 2) to conduct a randomized, active-controlled Phase 3 trial in patients with advanced UBC with overall survival as the primary endpoint. This Phase 3 trial is intended for conversion of MPDL3280A to full approval if this drug receives accelerated approval; 3) co-development of the PD-L1 IHC assay for which our CDRH colleagues have already been invited to provide feedback and/or advice during the process. Their current assessment is that validation performed for the assay is acceptable for a trial.

This development plan appears reasonable and supported by the encouraging preliminary evidence, and is similar to that I reviewed and experienced 4 years ago for the co-development of vemurafenib and a V600 mutation diagnostic for the treatment of advanced melanoma with BRAF V600E mutation. Given that the two trials mentioned above are planned to start in Q3 or 4 of this year, would recommend the sponsor to provide updated data with a longer follow up time (e.g., a minimum of 6 months by July) for the 65 patients already enrolled in the Phase 1 expansion cohort. This may help tune up the Phase 2 and or 3 trial design before initiation.

Please let us know if you have additional comments.

Max

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**From:** Woodcock, Janet

**Sent:** Thursday, May 08, 2014 4:26 PM

**To:** Benton, Sandra J; Temple, Robert; Jenkins, John K; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B; Hinton, Denise; Sacks, Leonard V

**Cc:** Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Robertson, Kim; Maher, Virginia E.; Ning, Yang-Min (Max); Ibrahim, Amna

**Subject:** RE: May 16, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 120827

I agree with division, but would be interested in what development plan is recommended. jw

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/s/  
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YANGMIN NING  
05/21/2014

VIRGINIA E MAHER  
05/22/2014

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 761034

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Genentech, Inc.  
Attention: Jerald Grace, PharmD  
Associate Program Director  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Grace:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Tecentriq® (atezolizumab).

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 25, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

*{See appended electronic signature page}*

Geoffrey Kim, MD  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** April 25, 2016; 3:00pm-4:00pm, EST  
**Meeting Location:** WO Bldg. #22; Conf. Room 1415 (t-con)

**Application Number:** 761034  
**Product Name:** Tecentriq® (atezolizumab)  
**Indication:** Urothelial Bladder Cancer  
**Sponsor/Applicant Name:** Genentech, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical:

- A timeline for submission of a report by April 15, 2016; this report will examine whether adverse events have been omitted from the datasets at other sites. In 3/30 patients inspected at Memorial, adverse events were missing from the AE dataset. The Applicant states that although these adverse events occurred in 2014, they were not entered into the eCRF until after the data cutoff in May 2015. All audit reports, corrective action plan(s) for any non-compliant sites, and how many sites required corrective actions during monitoring will be included in the report.
- Post-marketing requirements/commitments: Discuss the timelines for submission of the median duration of response from IMvigor 210.

**ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

**LCM AGENDA**

1. Introductory Comments – 5 minutes (Kim J. Robertson/V. Ellen Maher, MD)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

Each issue will be introduced by FDA and followed by a discussion:

- A timeline for submission of a report by April 15, 2016; this report will examine whether adverse events have been omitted from the datasets at other sites. The report will also include all audit reports, corrective action plan(s) for any non-compliant sites, and how many sites required corrective actions during monitoring.
- Post-marketing requirements and commitments

3. Discussion of Minor Review Issues – 10 minutes

- Labeling Concerns from the Applicant

4. Additional Applicant Data – 0 minutes (Applicant)

N/A

5. Information Requests – 10 minutes

Clinical:

- Please provide additional detail regarding the case of herpetic meningoencephalitis that occurred in patient 1283, including results of imaging and CSF studies (including serologies and titers if performed), and the outcome of the case. A case of immune-related meningoencephalitis is mentioned in section 5.5 of the USPI – if this did not occur in patient 1283, provide additional details regarding this case. Provide this information by April 22, 2016.
- Provide milestone dates for the PMRs/PMCs by April 22, 2016-done
- Provide the Division with a return USPI by April 22, 2016-done

6. Discussion of Upcoming Advisory Committee Meeting – 0 minutes

N/A

7. REMS or Other Risk Management Actions – 0 minutes

N/A

8. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

**PMRs:**

**CLINICAL:**

- Conduct a clinical trial to evaluate the effect of atezolizumab on thyroid function tests and clinical thyroid disease. Submit the completed report, datasets, and revised labeling.

**CMC:**

- Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that are expected to be present in samples at the time of patient sampling.

**PMCs:**

**CLINICAL:**

- Submit the median duration of response for all patients, all PD-L1 positive patients (IC 2/3), and all PD-L1 negative patients (IC 0/1) who responded to atezolizumab on IMvigor 210. Submit datasets and revised labeling concerning the median duration of response.

**CMC:**

- Perform supplemental characterization of the MCB to provide additional assurance that the cell bank was [REDACTED]<sup>(b) (4)</sup>. These data should include the evaluation of [REDACTED]<sup>(b) (4)</sup> and analysis with respect to growth characteristics and product quality.

**NON-CLINICAL:**

- Conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate time-points.

9. Major labeling issues – 0 minutes

N/A

10. Review Plans – 5 minutes

The Division anticipates it will continue its expedited review of the application, barring no unexpected shift in work priorities or team staffing. If unexpected significant issues arise during the course of the review, the review plan will default to normal priority review timelines. The timing of this review will, at this point, largely depend upon the extent to which adverse events have been omitted and whether new datasets are needed.

11. Wrap-up and Action Items – 5 minutes (TBD following LCM)

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/s/  
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GEOFFREY S KIM  
04/21/2016