CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761060Orig1s000
761060Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA #</td>
<td>BLA Supplement #</td>
<td></td>
</tr>
</tbody>
</table>

Proprietary Name: Mylotarg  
Established/Proper Name: gemtuzumab ozogamicin  
Dosage Form: intravenous

Applicant: Pfizer  
Agent for Applicant (if applicable):

RPM: Kris Kolibab, PhD  
Division: Division of Hematology Products

NDA Application Type:  
☐ 505(b)(1)  
☐ 505(b)(2)

Efficacy Supplement:  
☐ 505(b)(1)  
☐ 505(b)(2)

BLA Application Type:  
☐ 351(k)  
☒ 351(a)

Efficacy Supplement:  
☐ 351(k)  
☐ 351(a)

---

**For ALL 505(b)(2) applications, two months prior to EVERY action:**

- Review the information in the 505(b)(2) Assessment and submit the draft\(^2\) to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)

  - No changes
  - New patent/exclusivity (notify CDER OND IO)

  Date of check:

**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.

---

**Actions**

- Proposed action
- User Fee Goal Date is September 2, 2017

\(\boxed{\text{AP}}\)  \(\square\) TA  \(\square\) CR

- Previous actions (specify type and date for each action taken)

\(\square\) 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 [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain

\(\square\) Received

---

**Application Characteristics**\(^3\)

---

\(^1\) 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.

\(^2\) 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).

\(^3\) 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)
☐ Fast Track ☐ Rx-to-OTC full switch
☐ Rolling Review ☐ Rx-to-OTC partial switch
☒ Orphan drug designation ☐ Direct-to-OTC
☐ 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 required 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:

- Yes ☐ No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action ☑ Yes ☐ No
  - Indicate what types (if any) of information were issued
    ☐ None ☑ FDA Press Release ☐ FDA Talk Paper ☑ CDER Q&As ☒ Burst

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? ☒ No ☐ Yes
  - If so, specify the type

- Patent Information (NDAs only)
  - Patent Information:
    Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. ☒ Yes ☐ No
    ☐ Verified
    ☒ Not applicable because drug is an old antibiotic

**CONTENTS OF ACTION PACKAGE**

**Officer/Employee List**

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) ☑ Included
- Documentation of consent/non-consent by officers/employees ☑ Included
**Action Letters**

- Copies of all action letters *(including approval letter with final labeling)*  
  Approval letter 9-1-2017

**Labeling**

- **Package Insert** *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included 11-2-2016

- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** *(write submission/communication date at upper right of first page of each piece)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included

- **Labels** *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most recent draft labeling
    - Included 11-2-2016

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
  - Acceptability 1-17-2017
    - Reviews 8-14-2017 and 1-13-2017

- **Labeling reviews** *(indicate dates of reviews)*
  - RPM: 11-17-2016
  - DMEPA: 8-21-2017 and 7-5-2017
  - DMPP/PLT (DRISK):  
    - None
  - OPDP: 8-16-2017
  - SEALD:  
    - None
  - CSS:  
    - None
  - Product Quality:  
    - None
  - Other:  
    - None

**Administrative / Regulatory Documents**

- RPM Filing Review/Memo of Filing Meeting *(indicate date of each review)*
  - RPM Filing Review/Memo of Filing Meeting: 1-3-2017
  - Not a (b)(2)

- NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*
  - Completed *(Do not include)*

- Application Integrity Policy (AIP) Status and Related Documents
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP
    - Yes  
    - No

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
- **This application is on the AIP**
  - If yes, Center Director’s Exception for Review memo *(indicate date)*
  - If yes, OC clearance for approval *(indicate date of clearance communication)*

- **Pediatrics (approvals only)**
  - Date reviewed by PeRC _____
    - If PeRC review not necessary, explain: **Orphan Designation**

- **Breakthrough Therapy Designation**
  - 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.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*
  
<table>
<thead>
<tr>
<th>Month</th>
<th>Days</th>
</tr>
</thead>
</table>

- **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)

- **Minutes of Meetings**
  - If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*
    - N/A or no mtg
  - Pre-NDA/BLA meeting *(indicate date of mtg)*
    - 3/22/2016
  - EOP2 meeting *(indicate date of mtg)*
    - No mtg
  - Mid-cycle Communication *(indicate date of mtg)*
    - N/A
  - Late-cycle Meeting *(indicate date of mtg)*
    - N/A
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*
    - CMC 5-3-2017, CMC Pre-BLA (WRO) 9-28-2016, 11/21/2014
<table>
<thead>
<tr>
<th>Advisory Committee Meeting(s)</th>
<th>AC meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date(s) of Meeting(s)</td>
<td>7-11-2017</td>
</tr>
</tbody>
</table>

### Decisional and Summary Memos

- Office Director Decisional Memo *(indicate date for each review)*
  - None
- Division Director Summary Review *(indicate date for each review)*
  - 8-31-2017
- Cross-Discipline Team Leader Review *(indicate date for each review)*
  - 8-12-2017
- PMR/PMC Development Templates *(indicate total number)*
  - 10

### Clinical

- Clinical Reviews
  - Clinical Team Leader Review(s) *(indicate date for each review)*
    - None
  - Clinical review(s) *(indicate date for each review)*
    - 7-29-2017 (Original 1)
    - 7-28-2017 (Original 2)
  - Social scientist review(s) *(if OTC drug)* *(indicate date for each review)*
    - None
- Financial Disclosure reviews(s) or location/date if addressed in another review OR
  - If no financial disclosure information was required, check here □ and include a review/memo explaining why not *(indicate date of review/memo)*
    - Page 25 of 7-28-2017 primary review
- Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*
  - Pharmacovigilance memo 5-17-2017
- Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*
  - N/A
- Risk Management
  - REMS Documents and REMS Supporting Document *(indicate date(s) of submission)*
    - DRISK review 7-24-2017
  - REMS Memo(s) and letter(s) *(indicate date(s))*
  - 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)*
    - None
- OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*
  - Review: 6-24-2017
  - Letters: 7/28/2017; 5/23/2017 (2)

---

3 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
<table>
<thead>
<tr>
<th>Section</th>
<th>Review Result</th>
<th>Date/Signature Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Microbiology</strong></td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>Clinical Microbiology Review</td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>Statistical Division Director</td>
<td>None</td>
<td>Cosigned 7/28/2017 primary review</td>
</tr>
<tr>
<td>Statistical Team Leader</td>
<td>None</td>
<td>Cosigned 7/28/2017 primary review</td>
</tr>
<tr>
<td>Statistical Review</td>
<td>7/28/2017</td>
<td>Cosigned 7/28/2017 primary review</td>
</tr>
<tr>
<td><strong>Biostatistics</strong></td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td><strong>Clinical Pharmacology</strong></td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>Clinical Pharmacology Division Director Review</td>
<td>None</td>
<td>Cosigned 7/28/2017 primary review</td>
</tr>
<tr>
<td>Clinical Pharmacology Team Leader Review</td>
<td>None</td>
<td>Cosigned 7/28/2017 primary review</td>
</tr>
<tr>
<td>Clinical Pharmacology Review</td>
<td>7/28/2017</td>
<td>Cosigned 7/28/2017 primary review</td>
</tr>
<tr>
<td>OSI Clinical Pharmacology Inspection Review Summary</td>
<td>None requested</td>
<td>None hold</td>
</tr>
<tr>
<td><strong>Nonclinical</strong></td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>Pharmacology/Toxicology</td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>ADP/T Review</td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>Supervisory Review</td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>Pharm/tox review</td>
<td>7/31/2017</td>
<td>Cosigned 7/31/2017 primary review</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer</td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>Statistical review</td>
<td>None</td>
<td>None hold</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>None</td>
<td>Included in P/T review, page</td>
</tr>
<tr>
<td>OSI Nonclinical Inspection Review Summary</td>
<td>None requested</td>
<td>None hold</td>
</tr>
<tr>
<td>Product Quality</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td><strong>Product Quality Discipline Reviews</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tertiary review <em>(indicate date for each review)</em></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>- Secondary review (e.g., Branch Chief) <em>(indicate date for each review)</em></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>- Integrated Quality Assessment <em>(contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)</em></td>
<td>Cosigned 7/31/2017 review</td>
<td></td>
</tr>
<tr>
<td><strong>Reviews by other disciplines/divisions/Centers requested by product quality review team</strong> <em>(indicate date of each review)</em></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>*<em>Environmental Assessment (check one) (original and supplemental applications)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Categorical Exclusion <em>(indicate review date) (all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>Page 6 primary review 7-28-2017</td>
<td></td>
</tr>
<tr>
<td>- Review &amp; FONSI <em>(indicate date of review)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facilities Review/Inspection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Facilities inspections <em>(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</em></td>
<td>Acceptable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For all 505(b)(2) applications:</strong></td>
</tr>
<tr>
<td>- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
</tr>
<tr>
<td>- Finalize 505(b)(2) assessment</td>
</tr>
<tr>
<td>- For Breakthrough Therapy (BT) Designated drugs:</td>
</tr>
<tr>
<td>- Notify the CDER BT Program Manager</td>
</tr>
<tr>
<td>- For products that need to be added to the flush list (generally opioids): <strong>Flush List</strong></td>
</tr>
<tr>
<td>- Notify the Division of Online Communications, Office of Communications</td>
</tr>
<tr>
<td>- Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
</tr>
<tr>
<td>- If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
</tr>
<tr>
<td>- Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
</tr>
<tr>
<td>- Ensure Pediatric Record is accurate</td>
</tr>
<tr>
<td>- Send approval email within one business day to CDER-APPROVALS</td>
</tr>
<tr>
<td>- Take Action Package (if in paper) down to Document Room for scanning within <strong>two business days</strong></td>
</tr>
</tbody>
</table>

- No changes
- New patent/exclusivity (Notify CDER OND IO)
- Done
- Send email to CDER OND IO
- Done
- Done
- Done
- Done
- Done

Reference ID: 4148236
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
09/05/2017
Hello Brenda,

Please refer to BLA 761060 and the attached PI for your review.

Please review the changes/comments and do the following to the same draft:

- Please provide a response to the comments provided by the FDA
- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please officially submit the revised PI (in tracked changes and clean version word document) to the BLA and e-mail to me as soon as possible.

Please confirm receipt via email.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-----------------------------------------------
KRISTOPHER KOLIBAB
08/31/2017
Hi Brenda,

The Agency has no further comments on the PI received via email on August 31 at 3:56pm (EDT). Please submit this PI officially to the BLA as soon as possible.

Please confirm receipt.

Regards,
Kris

---

From: Kozan, Brenda W [mailto:Brenda.W.Kozan@pfizer.com]
Sent: Thursday, August 31, 2017 3:56 PM
To: Kolibab, Kristopher
Cc: Kozan, Brenda W
Subject: RE: BLA 761060 PI/Immediate Response is Requested/Please Confirm Receipt

Hi Kris,

Attached is the annotated and clean WORD addressing the comments below.

Please confirm receipt of this email.

Best regards,
Brenda

---

From: Kolibab, Kristopher [mailto:Kristopher.Kolibab@fda.hhs.gov]
Sent: Thursday, August 31, 2017 2:26 PM
To: Kozan, Brenda W
Subject: [EXTERNAL] BLA 761060 PI/Immediate Response is Requested/Please Confirm Receipt
Importance: High

Hello Brenda,

Please refer to BLA 761060 and the attached PI for your review. Please review the following changes:

1. All mentions of “newly diagnosed” revised to “newly-diagnosed”.

2. All cross references (outside of boxed warning) are listed before the period that ends the sentence.

3. All cross references that include multiple sections have “and” before the last section listed.
After you have made the changes, please officially submit the revised PI (in tracked changes and clean version word document) to the BLA and e-mail to me as soon as possible.

Please confirm receipt via email.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/31/2017
Hello Brenda,

Please refer to BLA 761060 and the attached PI for your review.

Please review the changes/comments and do the following to the same draft:

- Please provide a response to the comments provided by the FDA
- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please officially submit the revised PI (in tracked changes and clean version word document) to the BLA and e-mail to me by 3 PM (EDT) Wednesday, August 30, 2017.

Please confirm receipt via email.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB

08/30/2017
Hi Brenda,

Please refer to BLA 761060, Mylotarg. Please provide your response by **3PM EST Tuesday August 29, 2017** to the attached PMR/PMC document.

**Please confirm receipt via email.**

Regards,

Kris Kolibab, PhD  
*Senior Regulatory Health Project Manager*  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/29/2017
Hi Brenda,

The Agency is in agreement with the PMRs and PMCs and the schedule milestone dates. Please officially submit the PMR and PMC trials/studies to the BLA as soon as possible with a statement in the cover letter that you agree to perform the trials/studies as described and within the timelines you specify for the trials/studies.

Please confirm receipt.

Regards,
Kris

---

Hi Kris,

Please find attached the PMR PMC response doc.

Please confirm receipt of this email.

Best regards,

Brenda

---

Hi Brenda,

Please refer to BLA 761060, Mylotarg. Please provide your response by 3PM EST Tuesday August 29, 2017 to the attached PMR/PMC document.

Please confirm receipt via email.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/29/2017
Hi Brenda,

Please submit, as soon as possible and email to me, the source listing 16.2.6.1.2 and the SAS program t_efsd1c.sas used to generate Table 14.2.2.5.

Please confirm receipt.

Regards,
Kris

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/28/2017
Hello Brenda,

Please refer to BLA 761060 and the attached PI for your review.

Please review the changes/comments and do the following to the same draft:

- Please provide a response to the comments provided by the FDA
- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please officially submit the revised PI (in tracked changes and clean version word document) to the BLA and e-mail to me by 11 AM (EDT) Monday, August 28, 2017.

Please confirm receipt via email.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/23/2017
Hi Brenda,

Please refer to BLA 761060, Mylotarg. Please provide your response by **3PM EST Thursday August 24, 2017** to the attached PMR/PMC document.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.

**Please confirm receipt via email.**

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/22/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 3 PM (EDT) **Monday August 21, 2017** to the following information requests by email to me and officially submit to the BLA.

**Clinical Information Requests:**

1. Please provide Table 14.2.2.5 and Figure 14.2.2.1.15.

2. Please see attached information request.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
*Senior Regulatory Health Project Manager*  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
20 subjects had CRp during induction per investigator assessments, SUBJID listed below (subjects identified from dataset ADRS, PARAM="Investigator Response After Induction", AVALC="CRp")

The FDA exploratory analysis had EFS revised in these 20 subjects from EFS method D1 (PARAMCD='EFSD1S': investigator assessment, cutoff date 01Aug2011, IF date=date of randomization)
EFS censoring status variable CNSR changed to 0=not censored
EFS value variable AVAL changed to 1=day 1 as the event time

Analysis performed using dataset ADTTE with MITTFL='Y'

<table>
<thead>
<tr>
<th>Obs</th>
<th>SUBJID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/18/2017
Hi Brenda,

Please refer to BLA 761060, Mylotarg. Please provide your response by Noon EST Tuesday August 8, 2017.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.

PMC #4 Description: Re-evaluate gemtuzumab ozogamicin drug substance and drug product lot release acceptance criteria for appearance, iCE, CGE and cytotoxicity assays based on ≥25 unique combinations of gemtuzumab lots used to manufacture gemtuzumab ozogamicin drug substance and drug product using the commercial manufacturing process and tested using the commercial specification methods. Pfizer will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones:

<table>
<thead>
<tr>
<th></th>
<th>Final Protocol Submission:</th>
<th>Study/Trial Completion:</th>
<th>Final Report Submission:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MM/DD/YYYY</td>
<td>MM/DD/YYYY</td>
<td>MM/DD/YYYY</td>
</tr>
</tbody>
</table>

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.
2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
   b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
   c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

Please confirm receipt via email.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/07/2017
Hi Brenda,

Please refer to BLA 761060, Mylotarg. Please provide your response by Noon EST Thursday August 10, 2017.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.

PMR Safety in Children

PMR #3 Description: Provide data to confirm the safety of gemtuzumab ozogamicin in pediatric patients. Submit study report, including a data set, for Study AAML0531, a randomized trial of approximately 1000 pediatric patients with acute myeloid leukemia evaluating Mylotarg in approximately 500 pediatric patients.

PMR Schedule Milestones:

PMR Immunogenicity Binding

PMR #4 Description: Submit a validation report for a validated, sensitive, and accurate assay(s) for the detection of binding antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of binding antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay(s) should be able to detect and confirm binding antibodies directed against both gemtuzumab and the calicheamicin/linker moiety.

PMR Schedule Milestones:

Final Protocol Submission: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
PMR Immunogenicity Neutralizing

PMR #5 Description: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of neutralizing antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling.


PMR ADA

PMR #6 Description: Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to gemtuzumab ozogamicin with the validated assay developed under PMRs xxxx-xx.


Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
   b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
   c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

Reference ID: 4136110
Please confirm receipt via email.

Regards,

Kris Kolibab, PhD  
*Senior Regulatory Health Project Manager*  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
08/07/2017
Dear Ms. Kozan,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for BLA 761060, Mylotarg.

Please review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (do not reject any changes that the FDA proposed and do not delete any of the FDA’s comments)

After you have made any necessary changes, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST. Tuesday August 8, 2017.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

44 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ASHLEY S LUCCI VAUGHN
08/03/2017

Reference ID: 4134621
Good Afternoon Brenda,

For PMC 1 and PMC 2, our review team has updated the schedule milestones to reflect the Final Protocol Submission or Study/Trial Completion date. They have notified me that the [redacted] may not be modified as they would like the final report submission to be included in the Annual report. Please see update below:

Please refer to BLA 761060, Mylotarg. Please provide your response by **Noon EST Tuesday August 8, 2017**.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.

**PMR #1 Description:** Characterize the safety and pharmacokinetics of the 3 mg/m² day 1, 4, and 7 dose-schedule of Mylotarg as a single agent for treatment of patients with CD33-positive acute myelogenous leukemia. Submit a study report and dataset, including an analysis of hemorrhage, complete blood counts, PT, aPTT, and fibrinogen, hepatotoxicity, hepatic veno-occlusive disease (VOD), and the impact of hematopoietic stem cell transplantation pre- or post-Mylotarg on the incidence of VOD. Enroll at least [redacted] patients.

**PMR Schedule Milestones:**

<table>
<thead>
<tr>
<th>Desired Milestones:</th>
<th>MM/DD/YYYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft Protocol Submission:</td>
<td></td>
</tr>
<tr>
<td>Final Protocol Submission:</td>
<td></td>
</tr>
<tr>
<td>Study/Trial Completion:</td>
<td></td>
</tr>
<tr>
<td>Final Report Submission:</td>
<td></td>
</tr>
</tbody>
</table>

**PMR #2 Description:** Conduct a study to determine the effect of Mylotarg on the QT interval in humans.
Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
   b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
   c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

---

From: Kozan, Brenda W [mailto:Brenda.W.Kozan@pfizer.com]
Sent: Thursday, August 03, 2017 2:12 PM
To: LucciVaughn, Ashley
Subject: RE: UPDATED: PMR/PMC Review_ Response Required: BLA 761060/Mylotarg/ Pfizer/ Response by 12PM EST Tuesday August 8, 2017

HI Ashley,
I have one more question regarding PMC #1 72. The date for final report submission is is already completed. Since I do not have the timelines for the Final Protocol Submission or Study/Trial Completion I do not know if the date is reasonable. Can this date be modified?
Brenda

From: LucciVaughn, Ashley [mailto:Ashley.LucciVaughn@fda.hhs.gov]
Sent: Thursday, August 3, 2017 2:05 PM
Reference ID: 4134692
To: Kozan, Brenda W
Cc: Kolibab, Kristopher; Carioti, Theresa; Baird, Amy
Subject: [EXTERNAL] UPDATED: PMR/PMC Review_Response Required: BLA 761060/Mylotarg Pfizer/ Response by 12PM EST Tuesday August 8, 2017

Dear Ms. Kozan,

Please disregard the PMR/PMC Review email send 08/03/2017 at 1:37 PM EST. Please refer and respond to the current email.

Please refer to BLA 761060, Mylotarg. Please provide your response by Noon EST Tuesday August 8, 2017.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.

**PMR #1 Description:** Characterize the safety and pharmacokinetics of the 3 mg/m² day 1, 4, and 7 dose-schedule of Mylotarg as a single agent for treatment of patients with CD33-positive acute myelogenous leukemia. Submit a study report and dataset, including an analysis of hemorrhage, complete blood counts, PT, aPTT, and fibrinogen, hepatotoxicity, hepatic veno-occlusive disease (VOD), and the impact of hematopoietic stem cell transplantation pre- or post-Mylotarg on the incidence of VOD. Enroll at least patients.

**PMR Schedule Milestones:**

<table>
<thead>
<tr>
<th>Desired Milestones:</th>
<th>MM/DD/YYYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft Protocol Submission:</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Protocol Submission:</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Study/Trial Completion:</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Report Submission:</td>
<td>MM/DD/YYYY</td>
</tr>
</tbody>
</table>

**PMR #2 Description:** Conduct a study to determine the effect of Mylotarg on the QT interval in humans.

**PMR Schedule Milestones:**

<table>
<thead>
<tr>
<th>Desired Milestones:</th>
<th>MM/DD/YYYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft Protocol Submission:</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Protocol Submission:</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Study/Trial Completion:</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Report Submission:</td>
<td>MM/DD/YYYY</td>
</tr>
</tbody>
</table>

Reference ID: 4134692
**PMC #1 Description:**
To conduct the bioburden and endotoxin drug substance release method qualifications using two additional batches of drug substance.

**PMC Schedule Milestones:**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Study/Trial Completion</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>(b) (d)</td>
</tr>
<tr>
<td>Other: Annual Report</td>
<td>MM/DD/YYYY</td>
</tr>
</tbody>
</table>

**PMC #2 Description:**
To conduct the sterility and endotoxin drug product release method qualification using two additional batches of drug product.

**PMC Schedule Milestones:**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Study/Trial Completion</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>(b) (d)</td>
</tr>
<tr>
<td>Other: Annual Report</td>
<td>MM/DD/YYYY</td>
</tr>
</tbody>
</table>

**PMC #3 Description:**
Determine the effect of a broad range of concentrations of Mylotarg on the potential to inhibit platelet function by conducting in vitro studies on platelets and megakaryocytes. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

**PMC Schedule Milestones:**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desired Milestones</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Draft Protocol Submission</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Protocol Submission</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Study/Trial Completion</td>
<td>MM/DD/YYYY</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>MM/DD/YYYY</td>
</tr>
</tbody>
</table>

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show
YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR/PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
   b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
   c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ASHLEY S LUCCI VAUGHN
08/03/2017
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761060

INFORMATION REQUEST

Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB August 4th, 2017 in order to continue our evaluation of your application.

GEMTUZUMAB OZOGAMICIN DRUG SUBSTANCE

Section 3.2.S.2.2, Description of Manufacturing Process and Process Controls

2.
3.

If you have questions, call me, at (301) 348-3054.

Sincerely,

(See appended electronic signature page)

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Brenda,

Please refer to BLA 761060. Per the request of the review team please provide a response by **10 AM (EDT) Tuesday August 1, 2017** to the following container & carton comments by email to me and officially submit to the BLA.

**Container & Carton Comments:**

We have the following comments regarding your proposed container label and carton labeling submitted on July 17, 2017. We acknowledge your response to the Agency in the July 17, 2017 submission.

We determined from best labeling practices that the critical information in the labeling for the healthcare professional to appropriately prepare the product includes the volume of diluent required for reconstitution, the concentration of the reconstituted solution, and the volume (mL) and amount of drug (mg) that can be withdrawn and administered from the vial after reconstitution. We provide recommendations for the carton labeling to address your concerns.

**A. Container Label**

1. To address your concern that , add the concentration statement to the side panel. To accommodate this addition, unbold the storage statement and revise the side panel as follows:

   “Refrigerate vial at 2°C to 8°C (36°F to 46°F) in original carton to PROTECT FROM LIGHT. DO NOT FREEZE. See prescribing information for dosage, preparation, administration, and
storage. Concentration is 1 mg/mL when reconstituted with 5 mL Sterile Water for Injection, USP.”

**B. Carton Labeling**

1. Revise the inactive ingredient information to consistently reflect the labeled strength of the drug product as previously recommended in our June 28, 2017 comments:

   “Each single-dose vial delivers 4.5 mg gemtuzumab ozogamicin, dextran 40 (xx mg), sodium chloride (xx mg), sodium phosphate dibasic anhydrous (xx mg), sodium phosphate monobasic (xx mg), and sucrose (xx mg).”

2. Revise, as previously recommended in our June 28, 2017 comments, increase the prominence, and relocate the reconstitution information to a different side panel to increase the prominence of this critical information. To accommodate this, you may consider removing the Proprietary name, proper name, dosage form, and strength from the side panel that contains the storage information, place the reconstitution statement below the storage information, and the use the bolded heading “Reconstitution:” as follows:

   **Reconstitution:** Reconstitute with 5 mL Sterile Water for Injection, USP to obtain a concentration of 1 mg/mL that delivers 4.5 mL (4.5 mg). Gently swirl the vial to aid dissolution. Do Not Shake.”

*Please confirm receipt of this message via e-mail.*

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIRSTOPHER KOLIBAB
07/27/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **3 PM (EDT) Friday July 28, 2017** to the following information request by email to me and officially submit to the BLA.

**Clinical Information Request:**

1. Please submit to the BLA a letter of cross reference to NDA-21174 and IND-46635.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
**Senior Regulatory Health Project Manager**  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
07/27/2017
Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB July 28, 2017 in order to continue our evaluation of your application.

3.2. P.8 Stability


If you have questions, call me, at (301) 348-3054.

Sincerely,

{See appended electronic signature page}

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Brenda,

Please refer to protocol ALFA-0701 under BLA 761060 Mylotarg.

We request a response to the following FDA information request no later than Wednesday, **July 26, 2017, 3:00 PM EST**.

For ALFA-0701

1. Please clarify whether any patients received a dose reduction of any treatment drug.
2. Please indicate where in the datasets the variable for planned chemotherapy dose (per patient) can be found.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the BLA.

Let me know if you have any questions.

Best regards,
Rosa

(covering for Kris Kolibab)

--------------
Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

Reference ID: 4129709
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROSA J LEE-ALONZO
07/25/2017

Reference ID: 4129709
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **10 AM (EDT) Monday July 24, 2017** to the following information request by email to me and Rosa Lee-Alonzo and officially submit to the BLA.

**Clinical Information Request:**

Please provide a dataset for patients in ALFA-0701 with variables for occurrence of the following:

1. Prolonged thrombocytopenia
   a. Platelets < 50,000/m³ for >42 days from the start of the last induction cycle
   b. Platelets < 100,000/m³ for >42 days from the start of the last induction cycle
2. Prolonged neutropenia - ANC <500 for >42 days from the start of the last induction cycle

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
**Senior Regulatory Health Project Manager**  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
07/20/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 9 AM (EDT) Friday July 7, 2017 to the following information request by email to me and Rosa Lee-Alonzo and officially submit to the BLA.

Clinical Information Request:

1. In clinical trials including ALFA-0701 and the current Expanded Access Protocol, please describe how investigators are administering the 5mg maximum GO dose. Specifically, are they limiting each dose to one vial, or is a second vial being used in order to reach the 5mg dose?

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
06/29/2017
BLA 761060

INFORMATION REQUEST

Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB July 7, 2017 in order to continue our evaluation of your application.
Drug Substance – Product Quality

4.

Drug Product – Product Quality

5.

If you have questions, call me, at (301) 348-3054.
Sincerely,

[See appended electronic signature page]

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **3 PM (EDT) Friday June 30, 2017** to the following information request by email to me and Rosa Lee-Alonzo and officially submit to the BLA.

**Clinical Information Request:**

1. Please clarify what Mylotarg drug product was used in the MyloFrance-1 and AML-19 studies. Is the drug product used in those studies the same as you plan to market?

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
06/28/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the review team please provide a response by **3 PM (EDT) Friday July 7, 2017** to the following carton & container recommendations by email to me and Rosa Lee-Alonzo and officially submit to the BLA.

**A. General Comments**

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.
2. Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

**B. Carton Labeling**

1. Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h (Pearl River, NY 10965) as follows:
   
   Manufactured by Applicant on Form FDA 356h
   Address
   US License No. xxxx
   
   Remove (b)(4) from the License No. statement.

2. Revise the storage statement to read “Refrigerate vial at 2°C to 8°C (36°F to 46°F) in original carton. Do Not Freeze. Protect from light during storage, preparation, and administration.”
3. Revise the list of ingredients by placing the inactive ingredients in alphabetical order per USP General Chapters: <1091> Labeling of Inactive Ingredients followed by their quantitative information using the metric system of weight in parenthesis (xx mg) except for those inactive ingredients added to adjust pH or tonicity or water for injection.

   Additionally, revise the amounts of ingredients based upon how much is delivered in 4.5 mL of reconstituted solution. For example:
“Each single-dose vial delivers 4.5 mg gemtuzumab ozogamicin, dextran 40 (xx mg), sodium chloride (xx mg), sodium phosphate dibasic anhydrous (xx mg), sodium phosphate monobasic (xx mg), and sucrose (xx mg).

4. Per 21 CFR 610.61 (r), add the following statement to the side panel “No U.S. standard of potency”.

5. Revise the preparation instructions to read “Reconstitute with 5 mL Sterile Water for Injection, USP to obtain a concentration of 1 mg/mL that delivers 4.5 mL (4.5 mg). Gently swirl the vial to aid dissolution. Do Not Shake.”

6. Revise the statement “See prescribing information for dosage, preparation, administration, and storage.”

7. Remove the statement “.” We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word “not” can be overlooked and misinterpret the warning as an affirmative action. Additionally, increase the prominence of the route of administration on the principal display panel (PDP).

8. Include the statement “Reconstitution and dilution required “ on the Principal Display Panel (PDP). We recommend this to minimize the risk of administering the product as an intravenous bolus.

9. Include the net quantity statement (i.e. one vial) on the PDP in accordance with CFR 201.51.

10. Relocate the security logo on the principal display panel to the side panel as it takes readers’ attention away from important information such the route of administration.

11. The NDC number on the carton labeling and container label is usually the same when the quantity within the carton is equal to the quantity of the container. We note that the carton labeling has NDC and the container label NDC . Consider revising to have the same NDC number on the carton and container or provide your rationale for having different NDC numbers.

12. Clarify the significance of the number located next to the lot number and expiration date . If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due its close proximity to the lot number and expiration date.

C. Vial Container Label

1. Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h (Pearl River, NY 10965) as follows:

   Applicant on Form FDA 356h
   Address
   US License No. xxxx
Remove [REDACTED] from the License No. statement. Additionally, note that if the only manufacturer information on the labeling is the licensed manufacturer, then “Manufactured by” may be omitted to create space for other important information.

2. Relocate “Rx only” to appear at the top of the PDP to allow for addition and prominence of other critical information on the PDP.

3. If space permits, add preparation instructions to the side panel including final concentration after reconstitution as follows: “Reconstitute with 5 mL Sterile Water for Injection, USP for a concentration of 1 mg/mL and further dilute.”


5. Revise the statement [REDACTED] to read “See prescribing information for dosage, preparation, administration and storage” for usual dosage statement per 21 CFR 201.55 and 21CFR 201.100(b)(2).

6. Revise the storage statement from [REDACTED] to read “Refrigerate vial at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do Not Freeze.”

7. The NDC number on the carton labeling and container label is usually the same when the quantity within the carton is equal to the quantity of the container. We note that the carton labeling has NDC [REDACTED] and the container label NDC [REDACTED]. Consider revising to have the same NDC number on the carton and container or provide your rationale for having different NDC numbers.

8. Clarify the significance of the number located next to the lot number and expiration date [REDACTED]. If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due its close proximity to the lot number and expiration date.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
06/28/2017
Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB July 6, 2017 in order to continue our evaluation of your application.
GEMTUZUMAB OZOGAMICIN DRUG SUBSTANCE

Section 3.2.S.2.2, Description of Manufacturing Process and Process Controls

5.

6.

Section 3.2.S.2.5, Process Validation and/or Evaluation

7.

8.

Section 3.2.S.4.2, Analytical Procedures

9.

Section 3.2.S.4.3, Validation of Analytical Procedures

10.
If you have questions, call me, at (301) 348-3054.

Sincerely,

[See appended electronic signature page]

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 3 PM (EDT) Friday June 30, 2017 to the following information request by email to me and officially submit to the BLA.

Clinical Information Requests:

1. Please provide a tabular summary of simulated total hP67.6 antibody exposure and simulated unconjugated calicheamicin exposure (AUC and Cmax such as shown in Tables 24 and 25 of Module 2.7.2 Summary of Clinical Pharmacology) for the GO dose-schedule of 6 mg/m² on day 1 and 3 mg/m² on day 8.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------
KRISTOPHER KOLIBAB
06/21/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 3 PM (EDT) Friday June 16, 2017 to the following information requests by email to me and officially submit to the BLA.

**Clinical Information Requests:**

1. [Redacted]

2. Please provide protocols for the studies included in the IPD Meta-Analysis, or identify where in the submission these protocols can be found.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
06/08/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response to the following information requests by email to me and officially submit to the BLA. Please provide a response as soon as possible.

**Statistical Information Request:**

1. You have not provided an estimated Kendall’s tau for all 5 trials combined without using copula models. If the p-value from the cenken function is zero, please use a p-value down to the 15th decimal for conversion to standard error. It appears the 15th decimal is the limit for the p-value calculation in the function, the p-value of 0.00001 used by you previously may be too conservative.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
05/30/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 3 PM (EDT) Friday June 16, 2017 to the following information request by email to me and officially submit to the BLA.

**Clinical Information Requests:**

1. The rate of ≥Grade 3 hemorrhage events is considerably higher in the GO arm of ALFA-0701 than in other randomized trials of GO plus chemotherapy.
   a. For ALFA-0701, please provide an SAS dataset containing each adverse event pulled by SMQ Haemorrhages not including lab abnormalities that includes:
      i. USUBJID
      ii. Treatment arm
      iii. Preferred term
      iv. Grade of hemorrhage
      v. Concurrent platelet count (within 3 days of the event)
      vi. Action taken
      vii. AE outcome
   b. Using the data file in (a), please perform an analysis for ALFA-0701 to determine if the risk of hemorrhage is related to the platelet count at time of hemorrhage event. Please provide the proportion of patients who had a platelet count of <20,000/mm³ vs those with a platelet count ≥20,000/mm³ at the time of their hemorrhage event.
   c. For the events listed in the meta-analysis ALLTOX dataset, please identify which hemorrhage events were fatal.
   d. Page 151 of the ALFA-0701 CSR, Table 44 shows 27/131 patients in the GO arm and 12/137 patients in the No GO arm had a Grade 3-4 hemorrhage (as treated population). Page 108 of the Meta-Analysis CSR, Figure 42 shows 31/135 vs 12/136 patients with a Grade 3-4 hemorrhage. Please account for the 4 patient discrepancy and provide data regarding their events. Please update the data to include all fatal hemorrhages.
   e. Please provide an explanation for why hemorrhage rates were high in ALFA-0701 and what you plan to do to mitigate this risk.

2. We note that there is a trend towards decreased efficacy in ALFA-0701 for patients in the adverse/poor cytogenetic risk category. In order to perform a thorough risk-benefit analysis, it is important to determine whether patients with adverse risk cytogenetics who are also CD33 positive also fail to derive benefit from treatment with GO.
   a. Please provide an analysis of outcomes by CD33-positivity for patients in ALFA-0701 who have adverse cytogenetic risk. Include point estimates, 95% confidence intervals and HR or OR as applicable for the following:

<table>
<thead>
<tr>
<th>CR</th>
<th>EFS (defined as the occurrence of an event including relapse or death starting)</th>
<th>OS</th>
</tr>
</thead>
</table>

Reference ID: 4105044
<table>
<thead>
<tr>
<th>CD33 &lt;30%, Adverse cytogenetic risk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CD33 30-&lt;70%, Adverse cytogenetic risk</td>
<td></td>
</tr>
<tr>
<td>CD33 ≥70%, Adverse cytogenetic risk</td>
<td></td>
</tr>
</tbody>
</table>

b. Please perform this analysis in a greater number of patients using data from the trials in the meta-analysis (and including pediatric data) if possible.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  
Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
05/30/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by **12 PM (EDT) Friday May 26, 2017** to the following information request by email to me and officially submit to the BLA.

**Statistical Information Request:**

1. Please provide the programming code for the calculation of Kendall’s tau and its associated approximately 95% CI using the cenken function from software R library NADA.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
05/25/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by 10 AM (EDT) Thursday May 25, 2017 to the following information requests by email to me and officially submit to the BLA.

**Statistical Information Requests:**

1. Please provide estimated Kendall’s τ and Spearman’s ρ with 95% confidence interval for correlation between EFS and OS, for each individual trial and total combined of the 5 trials used for the EFS surrogacy analysis, without using the copula models.

2. Please clarify if information is available for trial ALFA-0701 regarding disease progression and treatment response besides CR/CRp.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
05/22/2017
BLA 761060

INFORMATION REQUEST

Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.  
Attention: Brenda W. Kozan  
Senior Manager, Worldwide Regulatory and Safety  
500 Arcola Road  
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB June 5, 2017 in order to continue our evaluation of your application.
If you have questions, call me, at (301) 348-3054.

Sincerely,

{See appended electronic signature page}

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **10 AM (EDT) Wednesday June 14, 2017** to the following information requests by email to me and officially submit to the BLA.

**Clinical Information Requests:**

1. Please confirm that all SUSARs reported postmarketing in Japan have been submitted to FAERS.

2. Our review of FAERS identified several adverse events Please review the cumulative postmarketing data and submit an analysis of the following unlabeled events from all sources, including post-marketing data and clinical trials:
   - Blood: thrombotic microangiopathy
   - Cardiac: cardiac failure, atrial fibrillation, myocardial infarction, torsade de pointes
   - Gastrointestinal: neutropenic colitis, pancreatitis
   - Hepatobiliary: Budd-Chiari syndrome
   - Immune: graft versus host disease
   - Infections: Pneumocystis jirovecii pneumonia, pulmonary mycosis, Stenotrophomonas infection
   - Renal: cystitis haemorrhagic, renal failure, acute kidney injury
   - Respiratory: pulmonary veno-occlusive disease, interstitial lung disease
   - Vascular: capillary leak syndrome

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
05/17/2017
Pfizer, Inc.
Attn: Alison Russell, Ph.D.
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to the meeting between representatives of your firm and the FDA on May 3, 2017.

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

If you have any questions please contact the Regulatory Business Project Manager, Andrew Shiber at 301-796-4798.

Sincerely,

{See appended electronic signature page}

Marjorie A. Shapiro, Ph.D.
Chief, Laboratory of Molecular and Developmental Immunology
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:  Meeting Minutes
MEETING MINUTES

Meeting Type: C
Meeting Category: CMC Only
Meeting Date and Time: May 3, 2017 12:00 P.M. Eastern Standard Time
Format: Teleconference

FDA, CDER, and the Office of Product Quality ATTENDEES:
Office of Biotechnology Products
Marjorie Shapiro, Ph.D. Chief, Laboratory of Molecular and Developmental Immunology
Sarah Kennett, Ph.D. Review Chief
Joel Welch, Ph.D. Review Chief
Gerald Feldman, Ph.D. Chief, Laboratory of Immunobiology
Mate Tolnay, Ph.D. Product Quality
Antonina Aydanian, Ph.D. Product Quality
Vicky Borders-Hemphill, Pharm.D. Quality Labeling

Pfizer, Inc.

1.0 BACKGROUND
Purpose of meeting: To discuss two BLA submissions from the applicant where there is a discrepancy in the extractable volume claims within both labeling presentations and the actual extractable volume after reconstitution.

2.0 DISCUSSION

Agency:
The applicant submitted labeling within BLA 761040 Besponsa (inotuzumab ozogamicin) and BLA 761060 Mylotarg (gemtuzumab ozogamicin) for extractable volume after reconstitution that does not accurately represent the deliverable amount of product. This is inconsistent with 21 CFR 201.51(g) and the 2015 Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products.

The Agency stated that the easiest remedy is for Pfizer to change all labels and labeling for the entire product presentation (vial labels, carton labeling, and prescribing information) for both products to reflect the accurate strength of the product per vial, the final concentration after reconstitution, the amount of diluent used to reconstitute, and the minimum deliverable volume after reconstitution.

Reference ID: 4094707
**BLA 761040 Besponsa (inotuzumab ozogamicin)**

For BLA 761040, per the labeling claim, after reconstitution the final concentration should be mg/mL with a deliverable volume of mL. Data submitted in the BLA do not reflect that a deliverable volume of mL can be withdrawn from the vial; therefore all labeling for the entire product presentation (vial labels, carton labeling, and prescribing information) should be changed to the accurate amount contained in the vial and the amount that can be extracted after reconstitution. The data submitted to BLA 761040 may be sufficient for the Agency to determine the appropriate amount to state on the label, but if additional information is available, it should be submitted to the BLA.

**BLA 761060 Mylotarg (gemtuzumab ozogamicin)**

For BLA 761060, per the labeling claim, after reconstitution the final concentration should be mg/mL with a deliverable volume of mL. No data were submitted to the BLA other than the statement in 3.2.P.2.2.1 “The average extractable volume was ml.” All labeling for the entire product presentation (vial labels, carton labeling, and prescribing information) should be changed to the accurate amount contained in the vial and the amount can be extracted after reconstitution. Submit sufficient data to the BLA that will help the Agency determine the appropriate amount to state on the label.

**Pfizer:**

Pfizer agreed that additional data regarding the extractable volume after reconstitution will be officially submitted to BLA 761060, and all labels and labeling claims for the entire product presentation will be changed to accurately reflect the amount contained in the vial and the extractable volume after reconstitution.

In addition, it is also agreed that the extractable volume after reconstitution data already submitted within BLA 761040 may be used to determine an accurate labeling claim, but additional extractable volume after reconstitution data may be submitted to BLA 761040. Pfizer agreed that all labels and labeling for the entire product presentation will be changed to accurately reflect the amount contained in the vial and the extractable volume after reconstitution that can be achieved as reflected by the data.

**Action items:**

Pfizer should submit information regarding extractable volume after reconstitution to both BLAs as soon as possible, but the Agency agreed that Pfizer should focus on BLA 761040, since this BLA has an earlier PDUFA deadline.

The Agency noted that the Division of Hematology Products, OHOP, has not yet communicated with Pfizer for either BLA regarding labeling and stated that Pfizer could expect Agency recommendations for these changes to the labels when DHP communicates proposed changes to the labels.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARJORIE A SHAPIRO
05/06/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 3 PM (EST) Monday May 1, 2017 to the following information requests by email to me and officially submit to the BLA.

**Clinical Information Requests:**

1. ALFA-0701 CSR Table 34 presents the incidence of predefined TEAE captured by the Sponsor (CHV).
   a. Please identify where in the datasets the data used to determine these numbers can be found.
   b. Please clarify whether or not there is data available on subsets of these predefined categories. For example, CSR p118 states broadly that “Pain” occurred in 14.5% of patients in the GO arm vs 3.6% in the control arm. Is there a breakdown of the incidence of individual types of pain that fall under the “Pain” category?

2. Regarding the definition of thrombocytopenia in ALFA-0701 – are the two uses below the same? i.e. is persistent thrombocytopenia as described here the same as “SAE” thrombocytopenia in the 2nd example (and all events coded as “thrombocytopenia” in the datasets)? If not, what is the difference between the two? Please clarify which (if any) uses laboratory data rather than reported AEs.
   a. ALFA-0701 CSR p48:  
      “Persistent Thrombocytopenia was defined as any Grade 3 or 4 Thrombocytopenia (platelets <50,000/mm3) which occurred in treated and responder patients and that did not resolve by the planned start date of the next cycle (or 45 days after Day 1 of second consolidation).”
   b. ALFA-0701 CSR p140 (and other pages)
      “All-causality SAEs experienced by >5% of patients in either treatment arm, by MedDRA Preferred Term, were:
      • Thrombocytopenia: 34 (26.0%) patients in the GO arm and 6 (4.4%) patients in the control arm.

3. In reference to the meta-analysis:
   a. We note that in two of the studies, patients in the No GO arm received GO after relapse/disease progression.
      i. How did you account for confounding in efficacy and safety analyses due to patients in the No GO arm receiving GO in consolidation or maintenance in AML15 and SWOG S01061 respectively?
      ii. Please identify where in the AE dataset there is a variable that denotes whether an AE occurred before or after Mylotarg salvage in the control arm, or provide an AE dataset with such a flag.
   b. Table 15 in your Meta-Analysis CSR p94 shows a statistically significant increase in “Neurologic” toxicity. What adverse events are included in your analysis of neurologic toxicity?
   c. The meta-analysis ALLTOX dataset contains columns related to “Oral.” Please define what AEs are included in this group.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products

Reference ID: 4088374
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
04/24/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **10 AM (EST) Thursday May 4, 2017** to the following information requests by email to me and officially submit to the BLA.

**Clinical Information Requests:**

Please address the following discrepancies between the PP and IWG responses for studies 202, 202, and 203 (table 9, SCE):

1. The below patients are said to have received other anti-leukemic therapy before the date of CR\textsuperscript{IWG}. Why should they be considered to have a CR if they received another therapy in the interim? Please clarify/explain the response determinations for these patients.

2. Several patients are noted to have met transfusion independence per IWG, but not per-protocol criteria. Although the IWG criteria do not specify a duration of transfusion independence, per protocol criteria required at least 1 week independence for platelets and 2 weeks for RBCs. We would not consider patients with durations of transfusion independence less than 1-2 weeks to be truly transfusion independent. How was transfusion independence defined per your IWG determination for the following patients?

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
04/20/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by **9 AM (EST) Friday April 14, 2017** to the following information requests by email to me and officially submit to the BLA.

**Statistical Information Requests:**

1. For each of the 5 individual trials used for the EFS surrogacy analysis, please provide estimated Kendall’s $\tau$ and Spearman’s $\rho$ for correlation between EFS and OS. The estimates should account for censoring in the EFS and OS endpoints.

2. Please add the listed survival variables (and associated censoring indicators) in the meta-analysis ANALYS dataset: EFS censored for SCT, EFS considering not achieving CR during the entire induction treatment period as a treatment failure event, and RFS censored for SCT.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration  

Tel: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
04/05/2017
Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB April 4, 2017 in order to continue our evaluation of your application.

If you have questions, call me at (301) 348-3054.

Sincerely,

(See appended electronic signature page)

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Reference ID: 4151802
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 9 AM (EST) Tuesday April 11, 2017 to the following information request by email to me and officially submit to the BLA.

Clinical Information Requests:

We are having difficulty determining the causes of death (COD) in your submission given that death data is spread across multiple datasets within the ISS. In addition, we would like to establish COD per a root cause analysis, particularly for early deaths and cases that may have been related to VOD. We would like to determine CODs for patients on pivotal studies 201, 202, and 203 (n=277), and relapsed/refractory patients receiving 9 mg/m^2 doses on studies 101, 103, and 100863 (n=61). Please provide a dataset in an xpt file containing CODs for these 338 total patients. Include at least the following variables:

1. Patient ID (PID)
2. Study number
3. Date of first dose of GO
4. Date of last dose of GO
5. Total number of doses of GO administered
6. Total number of courses of GO administered
7. Date of death
8. Date of last contact
9. Status at last contact (alive or dead)
10. Proximate cause of death
11. Root cause of death as determined by the sponsor (e.g. active AML, mylotarg-related, intercurrent illness)
12. Day of course on which death occurred, measured from day 1 of GO in that course (i.e. if death occurred following a second course of GO, count from day 1 of the second course of GO).
13. Flag indicating whether the death occurred within 28 days of the last dose of GO.
14. Flag indicating whether the patient had reported VOD at any point during the study or follow-up.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/28/2017
Hi Brenda,

We recognize that you have performed the evaluation of EFs surrogacy for OS based on requested EFS definition. However, we are also interested in the evaluation based on a slightly different definition of EFS. The difference is to consider an induction failure as failure to achieve a complete remission during the entire induction treatment, and not only limited to within 60 days of randomization. In addition, we would consider only CR, and not to include CRi/CRp, as a treatment success in the definition of EFS.

Please provide a response by **9 AM (EST) Wednesday April 5, 2017** to the information request by email to me and officially submit to the BLA.

Please confirm receipt.

Regards,

Kris

---

From: Kozan, Brenda W [mailto:Brenda.W.Kozan@pfizer.com]  
Sent: Thursday, March 23, 2017 5:11 PM  
To: Kolibab, Kristopher  
Subject: RE: BLA 761060/Stats IR/Due April 5

Hi Kris,  
The statistical review team is providing the following response to confirm the definition of EFS used the FDA had requested.

We confirm that the statistical evaluation of EFS surrogacy for OS presented in surrogate-endpt-rpt.pdf [Surrogate Endpoint Technical Report provided in BLA 761060; Sequence 0001 ] is using the requested EFS definition “EFS is defined as time from randomization to induction failure, relapse, or death due to any cause, whichever comes first. Induction Failure is defined as failure to achieve a complete remission within 60 days of randomization. For patients with Induction Failure, the date of induction failure is the randomization date” as described in Section 4.2. Section 4.1 describes that the data used was the individual patient data (IPD) meta-analysis data set (ANALYS), which implements the above definition for all 5 trials. The ALFA-0701 EFS definition was mentioned in Section 4.2 of the report only to note how the ALFA-0701 CSR EFS definition is different from the IPD meta-analysis EFS definition. However, we confirm the above requested EFS definition was used for ALFA-0701 trial in the analyses in this report.

In the suppl-surrogate-tech-endpt-rpt.pdf, in Listing 1.1 in the Appendix [Supplemental Surrogate Endpoint Technical Report on BLA 761060; Sequence 0006], the definition of EFS as reported from the literature source for each trial included in the analysis is provided. Only the 5 trials from the IPD meta-analysis used the exact EFS definition of “EFS is defined as time from randomization to induction failure, relapse, or death due to any cause, whichever comes first. Induction Failure is defined as failure to achieve a complete remission within 60 days of randomization. For patients with Induction Failure, the date of induction failure is the randomization date”. As noted in Section 3.3 of this supplemental report: For the 5 trials included in the IPD meta-analysis, the HRs for EFS and OS were estimated by Cox
proportional hazards model based on the individual patient data (surrogate-endpt-rpt.pdf, Table 2). Thus we confirm that the above requested EFS definition was used for ALFA-0701 trial in this supplemental report.

Based on this clarification, we believe that the analyses already conducted satisfy the below request.

Please confirm receipt of this email.

Best Regards,

Brenda W. Kozan
Sr. Manager
Worldwide Safety & Regulatory
Office (484)865-3586
Cell [821] 666-1081
Brenda.W.Kozan@pfizer.com

---

Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by 9 AM (EST) Wednesday April 5, 2017 to the following information request by email to me and officially submit to the BLA.

**Statistical Information Requests:**

1. Please repeat your analyses of EFS surrogacy for OS, as the ones presented in the surrogate-endpt-rpt.pdf and suppl-surrogate-tech-endpt-rpt.pdf files, using this definition of EFS: “EFS is defined as time from randomization to induction failure, relapse, or death due to any cause, whichever comes first. Induction Failure is defined as failure to achieve a complete remission within 60 days of randomization. For patients with Induction Failure, the date of induction failure is the randomization date”.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/24/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by **9 AM (EST) Wednesday April 5, 2017** to the following information request by email to me and officially submit to the BLA.

**Statistical Information Requests:**

1. Please repeat your analyses of EFS surrogacy for OS, as the ones presented in the surrogate-endpt-rpt.pdf and suppl-surrogate-tech-endpt-rpt.pdf files, using this definition of EFS: “EFS is defined as time from randomization to induction failure, relapse, or death due to any cause, whichever comes first. Induction Failure is defined as failure to achieve a complete remission within 60 days of randomization. For patients with Induction Failure, the date of induction failure is the randomization date”.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/23/2017
Hi Brenda,

Your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle.

Please confirm receipt.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277

Hi Kris,

With reference to the attached FDA labeling guidance document “Nonproprietary Naming of Biological Products” issued in January 2017 (see excerpt below), I am interested to know if gemtuzumab ozogamicin will be required to have a suffix (4 lowercase letters) included in the proper name designated by FDA at the time of licensure.

A. Prospective Naming of Biological Products Submitted Under Section 351(a) of the PHS Act

An applicant should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure (see section VI of this guidance). Such submissions can be made during the investigational new drug application (IND) phase16 or at the time of BLA submission. An applicant should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant’s preference. We recommend including any supporting analyses of the proposed suffixes for FDA’s consideration based on the factors described in this guidance.

Best Regards,
Brenda W. Kozan
Sr. Manager
Worldwide Safety & Regulatory
Office (484)865-3586
Cell (6)
Brenda.W.Kozan@pfizer.com
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/22/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by **9 AM (EST) Friday March 24, 2017** to the following information requests by email to me and officially submit to the BLA.

**Statistics Information Requests:**

Regarding the dataset ANALYS for individual patient data meta-analysis of EFS and OS:

1. Please clarify how to determine the specific types of EFS events (including: no CR during induction, relapse after CR, and death in CR) and types of OS events (including: death without CR, death after relapse, and death in CR) using the variables that are currently in the dataset. If the determinations cannot be made from the current dataset, please submit an additional dataset containing information for types of EFS and OS events.

2. Please clarify what is considered as a true CR in the variable column CCR.

3. Please clarify why the day variable columns DAYCRD, DAYDCR, DAYEFS, DAYR, and DAYREL contain negative values.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
OHOP/OND/CDER/FDA  

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/20/2017
Hello Brenda,

Please refer to BLA 761060 and the submission received on March 20, 2017 (eCTD 0024) which contains your responses and additional proposals related to the filing issues in the filing letter. The Agency has the following comment:

- We have no objection to your proposal to submit a revised PI at this time. We would request that the submission occur within the next 2 weeks. Please also provide a document with the justification to support the revisions.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/20/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **9 AM (EST) Friday March 24, 2017** to the following information requests by email to me and officially submit to the BLA.

**Clinical Information Requests:**

We need to determine whether patients in studies 201 to 203 met the inclusion criteria as stated in the protocol, i.e. ≥ 80% of the leukemic blasts had to have CD33 expression > 4 times that of baseline (as measured by the background fluorescence on that patient’s unstained cells). Thus, please address the following:

1. For studies 201 to 203, it appears that there are 4 patients with missing data for CD33 intensity at baseline and that only 1 patient had CD33 expression < 4 times that of background. Please confirm. If this is not correct, please provide information on missing data for CD33 intensity at baseline and any protocol violations for CD33 intensity less than 4 times that of background.

2. You note that the value “CD33_inten_very_dim” for the variable LBTEST represents the % of total leukemic cells. However, most of these values are below the threshold of 80%. It appears that 10 patients have missing data for this variable. Please describe this variable in detail, confirm the missing data, and explain why most values are less than 80%. If this is not the correct variable to determine the % of leukemic blasts that had CD33 expression > 4 times that of baseline, please direct us to the location where we can find this information.

**Please confirm receipt of this message via e-mail.**

Regards,

Kris Kolibab, PhD
**Senior Regulatory Health Project Manager**
**Division of Hematology Products**
**OHOP/OND/CDER/FDA**

*Phone: 240-402-0277*
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/17/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **12 PM (EDT) Monday March 20, 2017** to the following information request to me via email and officially submit to the BLA.

**Clinical Information Request:**

1. Please provide the protocol for the EORTC-GIMEMA AML-19 trial comparing GO to best supportive care in older patients with newly diagnosed AML.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/14/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 3 PM (EST) Friday March 17, 2017 to the following information requests and officially submit to the BLA.

**Clinical Information Requests:**

1. In the data file labimun.xpt, the lab tests (LBTEST data elements) listed as “CD33 INTENSITY OVER BACKGROUND” and “CD33_INTEN_VERY_DIM” have numerical results (variable LAB_RSLT) with N/A or % as the unit (LABUNITR), respectively.

   a) Please identify the units used for lab test “CD33 INTENSITY OVER BACKGROUND”. N/A is not sufficient.

   b) The range of results for “CD33_INTEN_VERY_DIM” vary from 0 to 126%. Please clarify what the percent is a percent of (i.e., what is the denominator) and explain why some of the percentages exceed 100%.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
KRISTOPHER KOLIBAB
03/13/2017

Reference ID: 4068771
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by **9 AM (EST) Friday March 17, 2017** to the following information requests by email to me and officially submit to the BLA.

**Statistical Information Requests:**

1. For Study ALFA-0701, please provide tabulations on concordance of EFS between investigator assessment and independent review for both 01August2011 and 30April2013 reference dates, and for with and without allowing up to 7 days as the window for agreement.

2. For Study ALFA-0701, please revise study report Table 20 to add 7 additional analyses of EFS for HSCT censored with 30April2013 as the reference date and for IR with IF date=randomization.

3. For the individual patient data meta-analysis of EFS as a surrogate for OS based on 5 GO trials, please provide estimated un-weighted and weighted R2 without using the copula models. Also please provide the estimated Surrogate Threshold Effect based on the individual patient data.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
**Senior Regulatory Health Project Manager**  
**Division of Hematology Products**  
**OHOP/OND/CDER/FDA**

**Phone: 240-402-0277**
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------------------

KRISTOPHER KOLIBAB
03/08/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 3 PM (EST) Friday March 10, 2017 to the following information requests and officially submit to the BLA.

Clinical Information Requests:

1. The numerous different blast-related variables are making it difficult to determine whether all patients included in ALFA-0701 were eligible to enroll on the study. Please create a custom data set with variables to establish diagnosis. At a minimum, this should include:
   a. Unique subject ID
   b. Treatment arm
   c. Blasts reported in CRF
   d. Blasts reported by IRC
   e. Blasts reported in labs
   f. Documentation of extramedullary disease at baseline
   g. LBDY, ADY

2. In your last IR response dated 2/28/17, you stated that BMBLASBL was the variable for baseline % blasts in bone marrow. However 18/271 patients do not have a value for this variable and another 16 patients have <20% blasts in their bone marrow at baseline. Allowing for patients who have either a ≥20% BMBLASBL value or diagnosis BLASTSIS LBORRES value OR ≥20% circulating blasts pretreatment, the 9 patients listed below still do not appear to meet diagnostic criteria for AML. Please justify including these patients in the study.

3. The treatment plan in Section 6.5 of the ALFA-0701 protocol provides transplant guidelines based CHV defined cytogenetic and molecular risk criteria– specifically, favorable and intermediate I = no transplant in 1st CR, intermediate II or unfavorable = transplant. CHV favorable + intermediate I seem to mirror the ELN favorable risk group. CHV intermediate II encompasses ELN intermediate I and II. However, the variables for CHV defined cytogenetics and the DOHNER variable for risk based on ELN Dohner 2010 do not detail which patients were Intermediate I and which were Intermediate II.
   a. Please create a custom data set with variables detailing which patients were:
      i. CHV Intermediate I
ii. CHV Intermediate II
iii. ELN Intermediate I
iv. ELN Intermediate II
v. Which achieved CRI
vi. Which went to transplant in CR1
vii. Which went to transplant in relapse

b. Please provide a separate subset analysis based on ELN favorable, intermediate I, intermediate II, and unfavorable subsets.

c. Your analyses based on ELN risk groups all used a combined favorable/intermediate group. Given the different treatment plans for patients who fall in the ELN favorable and intermediate I/II risk categories, please justify combining them in your analyses.

4. The CSR for study 100863 states that patient (b)(6) and (b)(6), had prior allogeneic bone marrow transplants. However, neither patient is listed in the file HSCT.xpt in the ISS dataset. Please clarify.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
03/06/2017
BLA 761060

INFORMATION REQUEST

Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB March 10, 2017 in order to continue our evaluation of your application.

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page
If you have questions, call me, at (301) 348-3054.

Sincerely,

{See appended electronic signature page}

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Brenda,

Please refer to BLA 761060 Mylotarg received on November 2, 2016, which provides for the proposed indications "indicated in combination with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia (AML) and treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy".

I have been notified by the Office of Hematology and Oncology Products that your drug will be discussed at the ODAC scheduled in July 2017. The meeting will take place either July 12 or 13. The Office of Advisors and Consultants will be in contact with you soon and will provide additional details. Also, please do not disclose this information to the public until the Federal Register notice has been published.

Please do not hesitate to contact me should you have any questions.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIRSTOHER KOLIBAB
03/01/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **3 PM (EST) Monday February 27, 2017** to information requests by email to me and officially submit to the BLA.

**Clinical Information Requests:**

1. Your submission contains only ALFA-0701 Version 5. Please provide the earlier protocol amendments and summaries of changes for ALFA-0701, or indicate where in the submission this information can be found.

2. The ALFA-0701 protocol states that the duration of follow-up is 2 years from the “date of last inclusion.” Please define “date of last inclusion.”

3. In your LBBONE dataset for ALFA-0701, please explain why the VISIT column is blank for more than half of the results.

4. Please explain how you defined which value is the baseline blast percentage for a patient. Also, explain the difference between blastosis (BLASTSIS) and blast/leukocytes (BLASTLE).

5. Please perform a post hoc subset analysis based on the revised 2017 ELN guidelines for risk stratification for genetics.

**Please confirm receipt of this message via e-mail.**

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
OHOP/OND/CDER/FDA  

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
02/21/2017
INFORMATION REQUEST

Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB February 22, 2017 in order to continue our evaluation of your application.

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page
If you have questions, call me at (301) 348-3054.

Sincerely,

{See appended electronic signature page}

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 10 AM (EST) Monday February 13, 2017 to information requests numbers 2-4 and by Monday March 6, 2017 for information request number 1 by email to me and officially submit to the BLA.

Clinical Information Requests:

1. Per our pre-BLA meeting held in March 2015, we asked that you include an ISE with detailed analyses of efficacy across your all clinical trials. However, your ISE analysis dataset for relapsed AML includes only 3 trials. Please add studies 0903A1-101-US, 0903A1-102-US, 0903A1-103-JA, 0903X-100374, and 0903X-100863 to the ISE analysis dataset.

2. The time to platelet recovery >100,000/µL for patients are listed as 41 and 26 days, respectively, in the data file recoviwg.xpt in your ISE analysis dataset, yet these patients are both listed as having CRp responses in the data file mxresiwg.xpt. Neither patient was censored. Please explain/clarify.

3. We are unable to clearly determine the column for duration of maximum response (REMDURAT?) in the data file subiwg.xpt in the ISE analysis dataset. Please clarify the definition of the column REMDURAT in subiwg.xpt for the ISE analysis dataset.

4. Please identify where we can find the duration of the first (prior) remission in months. We can see the categorical determinations in columns DUR_1REM and DUR1REMN in data file subiwg.xpt in the ISE analysis dataset, but would like the raw data in months.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
02/06/2017
BLA 761060

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Wyeth Pharmaceuticals Inc.
500 Arcola Road
Collegeville, PA 19426

ATTENTION: Brenda W. Kozan
Senior Manager Worldwide Regulatory and Safety

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin, 5 mg per vial.

We also refer to your correspondence, dated and received November 2, 2016, requesting review of your proposed proprietary name, Mylotarg.

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

If any of the proposed product characteristics as stated in your November 2, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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:

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager, in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Kristopher Kolibab, Regulatory Project Manager, in the Office of New Drugs, at (240) 402-0277.

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

/s/

TODD D BRIDGES
01/17/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the review team please provide a response by **11am (EST) Friday January 6, 2017** to the following information request by email to me and officially submit to the BLA.

**Information Requests:**

1. Provide detailed contact information and location for inspection for study monitoring and the Trial Master File documents for Study WS936568 (ALFA-0701 [MyloFrance 3]).

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
01/05/2017
Hi Brenda,

Please find attached the press release with FDA comments.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
OHOP/OND/CDER/FDA  

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
01/03/2017
Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer, Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Safety and Regulatory
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated November 2, 2016, received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Mylotarg (gemtuzumab ozogamicin), 5 mg/vial.

We also refer to your amendments dated November 7, 18, and 21; and December 6, 16, and 19, 2016.

We have administratively split your application into Original 1 and Original 2, which provides for the following indications:

- BLA 761060/Original 1 – Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia.
- BLA 761060/Original 2 – Treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

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 Standard. Therefore, the user fee goal date is September 2, 2017.

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 commitment requests by August 5, 2017. We are currently planning to hold an advisory committee meeting to discuss this application.

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

**Original-1**

1. The R^2 in the meta-analysis is only 0.45. This does not convincingly show support for EFS surrogacy for OS.

2. Your proposed indication is for the use of Mylotarg in “Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia.”

**Original-2**

1. You have proposed the indication “Treatment of patients with acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.”

2. 

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.
We request that you submit the following information:

**Clinical:**

1. We remind you that your response to our Information Request sent December 7, 2016 is due January 31, 2017.

**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 [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- 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.

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**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). 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 a request for advisory comments 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), and you believe the labeling is close to the final version.

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

**REQUIRED PEDIATRIC ASSESSMENTS**

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

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

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
01/03/2017
Hello Brenda,

Please refer to BLA 761060. Per the request of the statistical review team please provide a response by 9 AM (EST) Tuesday January 10, 2017 to the following information request by email to me and officially submit to the BLA.

**Statistical Information Requests:**

1. Provide analysis of EFS in Study ALFA-0701, with event date to be the date of randomization for patients who had failed induction treatment.

2. Provide clarification on the statistical software and programing codes used to generate Figure 1 and Figure 10 of the meta-analysis report.

3. Provide programming codes used to generate Tables 3, 4 and 5 of surrogate endpoint technical report. Also provide the trial level data, the definition of EFS for individual trials, and the programming codes used to generate supplemental surrogate endpoint technical report Table 2 and Figure 1.

**Please confirm receipt of this message via e-mail.**

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
OHOP/OND/CDER/FDA  

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
12/19/2016
INFORMATION REQUEST

Wyeth Pharmaceuticals Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologies License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB December 19, 2016 in order to continue our evaluation of your application.

1. Please provide an updated manufacturing schedule for [REDACTED] at the [REDACTED] manufacturing facility including details on the planned upstream and downstream operations for the campaign planned in [REDACTED].

2. Please update the FDA form 356H to include all manufacturing facilities.

If you have questions, call me, at (301) 348-3054.

Sincerely,

[See appended electronic signature page]

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Reference ID: 4151802
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **9am Tuesday January 31, 2017** to the following information requests by email to me and officially submit to the BLA.

**Information Requests:**

1. Please explain your reasoning for limiting the relapsed and refractory AML indication to adults 60 years and older when you have data in younger and pediatric patients.

2. Please explain your reasoning for not including pediatric patients in your newly diagnosed AML indication. The COG randomized control trial AAML0531 has data from over 1,000 patients. We recommend that you request the data from COG.

3. You have not presented a safety assessment based on all current worldwide knowledge regarding this product as you have excluded APL papers from your literature search. These assessments are relevant for safety as gemtuzumab is commonly used in this setting internationally and under expanded access.

4. Please submit the protocol for MyloFrance 1.

5. The PI for Site (b) in ALFA-0701 has reported >$83,000 income from consulting. The PIs for 6 of your remaining sites in your pivotal trial have not submitted financial disclosures. Please detail how you accounted for any bias in the efficacy endpoint that might have been introduced by investigators with conflicting financial interests.

**Please confirm receipt of this message via e-mail.**

Regards,

Kris Kolibab, PhD  
*Senior Regulatory Health Project Manager*  
*Division of Hematology Products*  
*OHOP/OND/CDER/FDA*

*Phone: 240-402-0277*
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
12/07/2016
BLA 761060

Wyeth Pharmaceuticals Inc.  
500 Arcola Road  
Collegeville, PA 19426

ATTENTION: Brenda W. Kozan  
Senior Manager Worldwide Regulatory and Safety

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin, 5 mg.

We acknowledge receipt of your correspondence, dated and received November 2, 2016, requesting a review of your proposed proprietary name, Mylotarg.

If the application is filed, the user fee goal date will be January 31, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager, in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Kristopher Kolibab, Regulatory Project Manager, in the Office of New Drugs, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Sue Kang, MS  
Team Leader, Project Management Staff  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Reference ID: 4019131
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUE H KANG
11/28/2016
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by 1pm Friday December 16, 2016 to the attached deficiencies by email to me and officially submit to the BLA.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
We have initiated review of BLA 761060, and we note that all required information has not been submitted, and that the organization of the application does not comply with eCTD. The following deficiencies must be resolved by December 16, 2016, in order for us to complete this initial review and determine whether your application can be filed.

1. You have placed SCE and SCS documents in folders under 5.3.5.3. SCE and SCS documents belong in Module 2. Efficacy analyses and data in Module 5 go under the ISE folder and Safety analyses and data in Module 5 go under the ISS folder. Please make the following corrections:

   a) The folder Study Report Body under 5.3.5.3 AML First Line highlighted below should be renamed as tables and figures and moved to either the ISE folder or to 2.7.3 AML First Line. It would be preferable to combine these figures and tables into a single pdf.

   b) The Study Report Body under 5.3.5.3 AML First Line highlighted below should be renamed as tables and figures and moved to the ISS folder. The Analysis Data folder should be moved to the ISS folder.
c) The Study Report Body under 5.3.5.3 AML in First Relapse highlighted below should be renamed as tables and figures and moved to either the ISE folder or to 2.7.3 AML in First Relapse. It would be preferable to combine these figures and tables into a single pdf. The Analysis Data folder should be moved to the ISE folder.

2. You have proposed the indication “Treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.” Identify where in the BLA you have submitted the clinical trial data.

3. You have proposed the indication “Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia (AML).” For your pivotal trial, ALFA-0701, you report that use of Mylotarg did not increase OS significantly, but you propose to use a limited meta-analysis to establish that EFS is a surrogate for OS. As indicated in our written advice on 8/30/2016, your analysis to establish surrogacy should include all randomized trials that are relevant whether they support or negate the surrogacy of EFS for OS. Identify where in the BLA you have submitted the literature search strategy for all randomized trials for first line treatment of AML and the meta-analysis of those trials to assess the role of EFS as a surrogate for OS.

4. Please provide a list of the foreign clinical trials in your application and identify the location of the information that addresses compliance with 21 CFR 312.120. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

5. In accordance with 21 CFR 314.106, please submit a statement of your rationale for assuming the applicability of foreign data to the U.S. population and U.S. medical practice, or identify where in the BLA this rationale can be found.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB  
11/18/2016
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **3pm Thursday November 17, 2016** to the following information request by email to me and officially submit to the BLA.

**Information Request:**

1. Please provide the contact information (Name, Address, Phone number, email, fax) for the where the sponsor’s files for ALFA-0701 and the meta-analysis can be found.

2. Please verify the accuracy of the following ALFA-0701 clinical site contact information for inspection of the clinical study records, including the medical records:

<table>
<thead>
<tr>
<th>Site # (Name, Address, Phone number, email, fax #)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site 03: Hervé Dombret</strong></td>
</tr>
<tr>
<td>AP-HP – Hôpital Saint Louis</td>
</tr>
<tr>
<td>1 avenue Claude Vellefaux</td>
</tr>
<tr>
<td>75010 Paris Cedex 10</td>
</tr>
<tr>
<td>France</td>
</tr>
<tr>
<td><a href="mailto:herve.dombret@sls.aphp.fr">herve.dombret@sls.aphp.fr</a></td>
</tr>
<tr>
<td>+ 33 1 42 49 96 43 (ph)</td>
</tr>
<tr>
<td>+ 33 1 42 49 93 45 (f)</td>
</tr>
</tbody>
</table>

| Site 05: Dominique Bordessoule  |
| CHU de Limoges – Hôpital Dupuytren  |
| 2 avenue Martin Luther King  |
| 87042 Limoges Cedex  |
| France  |
| borsessoule.URCH@chu-limoge.fr  |
| + 33 5 55 05 66 70 (ph)  |
| + 33 5 55 05 66 49 (f)  |

<p>| Site 19: Anne Vekhoff  |
| AP-HP – Hôpital Saint-Antoine  |
| 184 rue du Faubourg Saint-Antoine  |
| 75571 Paris Cedex 12  |
| France  |
| <a href="mailto:anne.vekhoff@sat.aphp.fr">anne.vekhoff@sat.aphp.fr</a>  |
| + 33 1 42 34 85 86 (ph)  |
| + 33 1 49 28 32 00 (f)  |</p>
<table>
<thead>
<tr>
<th>Site # (Name, Address, Phone number, email, fax #)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 08: Thierry De Revel</td>
</tr>
<tr>
<td>H.I.A. Percy</td>
</tr>
<tr>
<td>101 avenue Henri Barbusse</td>
</tr>
<tr>
<td>92140 Clamart</td>
</tr>
<tr>
<td>France</td>
</tr>
<tr>
<td>Email:</td>
</tr>
<tr>
<td>+ 33 1 41 46 63 03 (ph)</td>
</tr>
<tr>
<td>+ 33 1 41 46 64 55 (f)</td>
</tr>
</tbody>
</table>

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
11/16/2016
BLA 761060/Original 1
BLA 761060/Original 2

BLA ACKNOWLEDGMENT

Pfizer, Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Safety and Regulatory
500 Arcola Road
Collegeville, PA  19426

Dear Ms. Kozan:

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 Product: Mylotarg (gemtuzumab ozogamicin)
Date of Application: November 2, 2016
Date of Receipt: November 2, 2016

Our Reference Number: BLA 761060

BLA 761060 provides for the use of Mylotarg (gemtuzumab ozogamicin) lyophilized cake or powder, 5mg/vial for the following indications which, for administrative purposes, we have designated as follows:

- BLA 761060/Original 1 – Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia.
- BLA 761060/Original 2 – Treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

All future submissions to your BLA should specify the BLA number and all Original numbers to which each submission pertains.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 1, 2017, in accordance with 21 CFR 601.2(a).

Reference ID: 4013345
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).

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

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

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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have questions, call me at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
11/14/2016
BLA 761060

Wyeth Pharmaceuticals Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated and received November 2, 2016, submitted under section 351(a) of the Public Health Service Act for Gemtuzumab Ozogamicin.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB November 21, 2016 in order to continue our evaluation of your application.

Please provide an update on the manufacturing schedules for the Gemtuzumab Ozogamicin drug substance and drug product at Wyeth Pharmaceutical.

If you have questions, call me, at (301) 348-3054.

Sincerely,

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Brenda,

Please refer to BLA 761060. Per the request of the clinical review team please provide a response by **2pm Friday November 4, 2016** to the following information request by email to me and officially submit to the BLA.

**Information Request:**

1. Please identify the folder that contains the ISS data set.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
OHOP/OND/CDER/FDA

*Phone: 240-402-0277*
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
11/03/2016
Dear Ms. Kozan:

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

We also refer to your submission dated July 8, 2016, containing a Type B Pre-BLA meeting request. The purpose of the requested meeting was to gain agreement with the Division regarding the Chemistry, Manufacturing, and Control (CMC) information to be included in a Biologics License Application (BLA).

Further reference is made to our Meeting Granted letter dated August 11, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your July 8, 2016, background package.

If you have any questions, call me at (240) 402-0277.

Sincerely,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses
WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Other
Application Number: IND 046635
Product Name: Mylotarg (gemtuzumab ozogamicin for injection)
Indication: Treatment of patients with untreated, de novo Acute Myeloid Leukemia (AML) and AML in first relapse.
Sponsor/Applicant Name: Pfizer, Inc.
Regulatory Pathway: §351 of the Public Health Service Act

1.0 BACKGROUND

Pfizer, Inc. requested a type B Pre-BLA meeting with FDA on July 8, 2016, to gain agreement with the Division regarding the Chemistry, Manufacturing, and Control (CMC) information to be included in a Biologics License Application (BLA).

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (recombinant humanized immunoglobulin (Ig) G4, kappa antibody produced by mammalian cell culture in NS0 cells) that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. The antibody portion binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells.

On August 11, 2016, FDA sent Pfizer, Inc. the written responses only granted letter.

2.0 QUESTIONS AND RESPONSES

2.1. Questions

Question 1:

Does the Agency concur with the plans regarding immunogenicity analyses?

FDA Response to Question 1:

Our expectation is that validated immunogenicity screening, confirmatory and neutralizing assays will be submitted with a BLA package. Clarify your plans to submit immunogenicity data and assay validation reports to the BLA. Were the original immunogenicity assays used to assess ADA in patients in the clinical trials that will support the BLA submission? Provide a timeline for completion of validation of the ADA assays and analysis of clinical samples relative to your planned submission of the BLA.
**Question 2:**

Does the Agency agree with the proposed Module 3 Table of Contents and level of granularity?

**FDA Response to Question 2:**

We agree with the proposed Module 3 Table of Contents to contain [3.2.S sections, (b) (4) and one for gemtuzumab ozogamicin drug substance, as well as one 3.2.P section describing gemtuzumab ozogamicin drug product.

We also agree with the proposal to cross reference to the [DMF# (b) (4) submitted in December 2015.

Provide a letter of cross reference in Module 1 and a genealogy table that will link the [batch history, (b) (4) batches with the appropriate drug substance and drug product batches used in non-clinical and clinical development, process validation and the proposed commercial process. The table should include manufacturing date and site, scale and links to appropriate drug substance and drug product sections for release and stability data.

We also note your statement “Pearl River site information, including [processing and validation information, will be provided in a site specific DMF.” Please be aware that although a Type V DMF is appropriate for facility specific information, and we recommend that it contain information regarding cleaning validation and potential cross-over contamination of highly potent drug substance and drug product. [processing and sterilization validation studies and information specific for gemtuzumab ozogamicin drug product should be submitted to the BLA. Please also refer to the additional comments provided below.

**Question 3:**

Does the Agency agree that the DP stability sections can be updated during BLA review (as indicated in ICH Q5C)?

**FDA Response to Question 3:**

We agree that the drug product stability sections can be updated with additional stability data during BLA review, for up to month 7 for a standard submission and month 4 for a priority submission. For any stability update, please use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any). The determination of an expiration dating period will be a BLA review issue.
Additional Comments:

We remind you of the advice discussed at the CMC pre-BLA meeting held on November 2014. We are also providing updated product quality microbiology comments for you to consider for the preparation of your BLA 351(k) submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance sections of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- 
- 
- 
- 
- 
- 
- 
- 
- 
- 
- 
- 
- 
- 
- 

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the aseptic process and sterility assurance. For guidance on the type of data
and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”.

The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:
The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry.

- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed (if applicable) and the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

- Microbiological studies in support of the post-reconstitution and post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during reconstitution and dilution. The test should be run at the label’s recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations which would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-reconstitution plus post-dilution storage period is not more than 48 hours at 2-8°C.

Regarding the we recommend that you reassess the clonality of the MCB or current WCB. If the MCB/ WCB is not clonal, it is possible a cell containing the could have a slight growth advantage and increase its representation in the total cell population over time.
3.0 OTHER MEETING INFORMATION

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. 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 PLLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- 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
- 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 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```
   [m5]
   datasets
   bimo
   site-level
```

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.

¹ 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

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTOPHER KOLIBAB
09/28/2016
IND 046635

Pfizer, Inc.
Attention: Jaimie Walsh, MS
Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA  92121

Dear Ms. Walsh:

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

We also refer to the meeting between representatives of your firm and the FDA on March 22, 2016. The purpose of the meeting was to discuss the totality of evidence that will be provided in the Biologics License Application (BLA) submission.

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

If you have any questions call, Kris Kolibab, Senior Regulatory Project Manager at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: March 22, 2016; 10:00 AM – 11:00 AM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 046635
Product Name: Mylotarg (gemtuzumab ozogamicin)
Indication: Acute Myeloid Leukemia
Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: Albert Deisseroth, MD, PhD
Meeting Recorder: Kris Kolibab, PhD

FDA ATTENDEES
Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP):
Ann T. Farrell, MD, Division Director
Albert Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Reviewer
R. Angelo de Claro, MD, Clinical Team Leader
Rosanna Setse, MD, Clinical Reviewer
Yvette Kasamon, MD, Clinical Reviewer
Kris Kolibab, PhD, Senior Regulatory Project Manager

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V:
Gene Williams, PhD, Clinical Pharmacology Team Leader
Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics V (DBV):
Lei Nie, PhD, Statistics Team Leader
Yun Wang, PhD, Statistics Reviewer

SPONSOR ATTENDEES
Rebecca Benner, PhD, Biostatistics

Reference ID: 3907895
Mace Rothenberg, MD, Chief Medical Officer, Clinical Development & Medical Affairs
Stephen Rubin, MD, Clinical
Beverly Knight, PhD, Clinical Pharmacology
Reza Khosravan, PhD, Clinical Pharmacology
Leena Das Young, PharmD, Late Phase Strategy, Development, Submission, and Lifecycle
Management Group, Vice President
Nathalie Bouxin, PhD, Late Phase Development
Mark Shapiro, MD, PhD, Medical Affairs
Caroline Henesey, PhD, Regulatory Strategy
Jaimie Walsh, MS, Regulatory Strategy
Jeanette Preston, MD, MPH, Safety Surveillance and Risk Management
Douglas Laird, PhD, Translational Oncology

1.0 BACKGROUND

Pfizer, Inc. requested a type C meeting with FDA on January 13, 2016, to provide an update on the totality of evidence that will be provided in the Biologics License Application (BLA) submission for gemtuzumab ozogamicin. This will include an update of the results from the pivotal MF3 study, including confirmation of the investigator event-free survival (EFS) and relapse-free survival (RFS) results by an independent review, and the results from the IPD Meta-Analysis.

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (recombinant humanized immunoglobulin (Ig) G4, kappa antibody produced by mammalian cell culture in NS0 cells) that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. The antibody portion binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells.

FDA sent Preliminary Comments to Pfizer, Inc. on March 14, 2016.

2. DISCUSSION

2.1. Questions

Question 1:

Does the FDA agree that

FDA Response to Question 1:

No. This will be a review issue.

Discussion:
**Question 2:**

To further characterize GO in de novo AML, Pfizer is considering a study that would allow for the expeditious collection of pharmacokinetics (PK), exposure-response, QTc, and anti-drug antibody (ADA) data with the fractionated dosing regimen (3x3 mg/m2) in combination with the 3+7 DNR/AraC regimen for induction and consolidation therapy in patients with de novo AML. Does the FDA consider further characterization of GO desirable and, if so, is this a reasonable approach?

**FDA Response to Question 2:**

We cannot comment on whether “further characterization” is needed, as you have not provided us with a summary of what characterization has already been completed. We reiterate our current expectations for the clinical pharmacology development of antibody-drug conjugates which was provided to you at the Type C meeting on November 8, 2012, and are as follows:

1. Conduct population pharmacokinetic analysis to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of GO, total hP67.6, unconjugated calicheamicin and its metabolites in humans. Explore the exposure-response relationships for GO, total hP67.6, unconjugated calicheamicin and its metabolites for measures of both effectiveness and toxicity. Refer to Guidances for Industry Population Pharmacokinetics and Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications for more information.

2. Validate the analytical methods used to determine the concentrations of GO, the total hP67.6, and unconjugated calicheamicin and its metabolites. Refer to the Guidance for Industry Bioanalytical Method Validation.

3. Evaluate the impact of immunogenicity on the pharmacokinetics, pharmacodynamics, safety and efficacy of the GO and total hP67.6.

4. Evaluate the in vitro ability of the calicheamicin (and its metabolites) to act as substrates, inhibitors or inducers of cytochrome P450 enzymes, conjugating enzymes and transporters to determine the need for drug interaction trial(s). Refer to the Drug Interaction Studies Guidance for more information.

5. Identify the pathways by which calicheamicin and its metabolites are eliminated and excreted to determine the need for organ impairment trial(s). Please refer to the Guidances for Industry Pharmacokinetics in Patients with Impaired Renal Function and Pharmacokinetics in Patients with Impaired Hepatic Function for more information.

6. Evaluate QT/QTc interval prolongation potential of GO. In oncology, alternative proposals to the “TQT” trial may be appropriate. Submit your overall QT risk evaluation plan for FDA review. For more information, refer to the Guidance for Industry entitled E14 Clinical Evaluation of QT/QTc Interval Prolongation.
We recommend that you submit a summary of what characterization has been done, what *in vitro* and *in vivo* data has been acquired, a synopsis of the study being planned, and include specific questions for the FDA to address.

**Discussion:**

FDA noted that the meeting package did not have detailed reviews of clinical pharmacology data such that FDA was able to review and draw conclusions that differed from the past conclusions from the pre-BLA meeting of March 2015. The question of whether accumulated QT data will be sufficient was unclear, but exposure response analyses including QT as an endpoint have been performed for a related ADC and are intended to be submitted.

**Post meeting note:**

FDA will review the recommendations made at the March, 2015 meeting together with the information received Friday March 18, 2016 and forward a summary to Pfizer.

**Question 3:**

A. Based on the redundancy between the current drafts of the GO Summary of Clinical Efficacy (SCE) and the Integrated Summary of Efficacy (ISE), Pfizer proposes to include a separate SCE for each indication that will include detailed and integrated analyses of efficacy (positive, negative or incomplete) across all clinical trials as well as from the published literature. The IPD Meta-Analysis Report, which provides the integrated analysis for patients with previously untreated, de novo AML, will be included in Module 5 and summarized in the SCE/Summary of Clinical Safety (SCS) documents. Does the FDA agree with this approach?

**FDA Response to Question 3A:**

Yes.

B. In order to present a meaningful and complete safety profile for GO with the single-agent safety data in relapse AML patients providing a foundation for GO used in combination with DNR/AraC in the de novo AML setting, Pfizer proposes to develop a single, combined Integrated Summary of Safety (ISS) and a single, combined SCS, each including both indications. Does the FDA agree with this approach?

**FDA Response to Question 3B:**

Yes, but please plan to include in each file in the ISS data set a variable denoting whether the row applies to the de novo or to the relapsed AML indication. Also, the ISS lab files are frequently too large to submit through the gateway and must be split. Please also describe how you plan to split the ADLB domain in the ISS data set.

**Discussion:**
No discussion occurred.

**Question 4:**

*Given the totality of data from the pivotal ALFA 0701 study, the IPD meta-analysis and the data from the relapsed AML population, which demonstrate a favorable benefit-risk profile for GO in patients with AML, a serious condition with an unmet medical need, Pfizer would like to submit an application for Fast Track in order to enable a Rolling Review for the GO BLA. Does the FDA agree that the available clinical data demonstrate the potential for Mylotarg to address an unmet medical need and that an application for Fast Track Designation could be submitted?*

**FDA Response to Question 4:**

*We would have no objection to your plan to submit a request for Fast Track Designation. Please be certain to include in the request a description of a clinical development plan that will support regular approval.*

**Discussion:**

FDA agreed that the current available studies could be the basis for the fast track designation request, but the application will need to address the issues discussed in question 1.

**Additional Clinical Comments:**

1. Please note that except where specified, the advice provided in this meeting should be considered additional to rather than in lieu of the advice provided in prior meetings regarding the content of the BLA.

2. We have viewed your draft SCE Tables of Contents and ISS Table of Contents. We understand that these are very high overviews, but we have the following comments on your proposals:

   a) In the SCEs, please ensure that the subgroup analyses address at least age, gender and race (21 CFR 314.50(d)(5)(v)) among the demographic factors.

   b) You propose [redacted]. We suggest that you include MyloFrance 1 in the SCE for relapsed AML. The response rate in cycle 1 is relevant for the analysis of dosing information for the relapsed AML indication.

   c) In the subsection 2.7.3.3.2 on the SCE for the de novo AML indication, you propose to [redacted]. We suggest that there may be adequate and well-controlled studies in the literature that should be taken into account in the comparison of efficacy across results of all studies, and these may affect your conclusion.
d) For the SCE for treatment of relapsed AML, please include an assessment of duration of response. For this outcome, describe any differences between studies in how patients were monitored for relapse, since this may contribute to interstudy differences for this outcome.

**Additional Statistics Comments:**

1. In Study ALFA-0701, it is not clear how multiplicity was controlled in testing secondary endpoints. According to the listing order of secondary objectives in Section 10.1.1, the first secondary endpoint CR + CRp rate. According to the secondary efficacy evaluations Section 10.1.4.3 or background Section 6, the first secondary endpoint was overall survival. Neither OS nor CR + CRp rate was statistically significant.

2. Please clarify your disease assessment schedules in study ALFA-0701.

3. Please include descriptive statistics, such as median, for the overall survival, EFS or other time-to-event endpoints in your meta-analysis.

**Discussion:**

The FDA and the sponsor discussed the possibility and values of submitting mock datasets for the meta-analyses of OS prior to the NDA submission. The sponsor plans to submit them to the IND. The FDA also suggested the sponsor document the incidences and possible causes for the discrepancies between EFS per investigator and EFS per IRC in their clinical study report.

**Post meeting note:**

The mock datasets for OS should include the names and definitions of the variables that will be used in real meta-analysis, and they should follow data standard as much as possible. Both EFS per IRC and EFS per investigator data should be submitted.

**3.0 OTHER MEETING INFORMATION**

**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 (EOP) 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. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/Development ApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor provided the attached handout for the meeting.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISEROTH
03/25/2016
IND 46635

Wyeth Pharmaceuticals, Inc., a Pfizer Company  
Attention: Jaimie Walsh  
Associate Director, Worldwide Safety and Regulatory  
10646 Science Center Drive  
San Diego, CA 92121

Dear Ms. Walsh:

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

We also refer to the meeting between representatives of your firm and the FDA on November 21, 2014. The purpose of the meeting was to discuss and gain agreement on the proposed CMC package to support re-registration of gemtuzumab ozogamicin.

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

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.  
Chief, Laboratory of Molecular and Developmental Immunology  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: CMC Only

Meeting Date and Time: November 21, 2014 12:00 PM – 1:00PM
Meeting Location: FDA White Oak
Meeting Format: Face to Face

Application Number: IND 46635
Product Name: gemtuzumab ozogamicin
Sponsor/Applicant Name: Wyeth Pharmaceuticals, A Pfizer Company

Meeting Chair: Marjorie Shapiro, Ph.D.
Meeting Recorders: Melinda Bauerlien, M.S.

FDA ATTENDEES:

Center for Drug Evaluation and Research
Office of Biotechnology Products (OBP)
- Marjorie Shapiro, Ph.D. Team Leader, Division of Monoclonal Antibodies (DMA)
- Antonina Aydanian, Ph.D. Product Quality Reviewer, DMA
- Emanuela Lacana, Ph.D. Policy, OBP
- Melinda Bauerlien, M.S. Senior Regulatory Project Manager, OBP

Office of New Drug Quality Assessment (ONDQA)
- Janice Brown, M.S. Team Leader
- Danuta Gromek-Woods, Ph.D. Product Quality Reviewer
- Ali Al Hakim, Ph.D. Branch Chief

Office of Compliance/Biotech Manufacturing Assessment Branch (BMAB)
- Patricia Hughes, Ph.D. Team Leader, BMAB
- Colleen Thomas, Ph.D. Microbiologist, BMAB
- Bo Chi, Ph.D. Microbiologist, BMAB

Office of Compliance/New Drug Manufacturing Assessment Branch (NDMAB)
- Robert Wittorf, Pharm.D. Product Quality Reviewer

SPONSOR ATTENDEES
- Sandra Meech, M.D. Senior Director, Clinical
- Jaimie Walsh, M.S. Director, Regulatory
- Nathalie Hayduk, M.S. Director, Co-development lead
- Jaclyn Moxham, M.S. Director, Regulatory CMC
- Leslie Bloom, Ph.D. Executive Director, Regulatory CMC

Reference ID: 3683254
1.0 BACKGROUND

Name of drug: gemtuzumab ozogamicin

Indication: Gemtuzumab ozogamicin, in combination with daunorubicin (DNR) and cytarabine (Ara-C), is indicated for patients with previously untreated, de novo acute myeloid leukemia (AML) [b] (b) [4]

Objectives: To discuss and gain agreement on the proposed CMC package to support re-registration of gemtuzumab ozogamicin.

Preamble
We understand that you have submitted a request for designation (RFD) to resubmit a marketing application for gemtuzumab ozogamicin as a Biologics Licensing Application (BLA) rather than a New Drug Application (NDA). Although the Agency has not yet made a final determination regarding your request, we are responding to the questions in this meeting package as if the application will be submitted as a BLA.

According to 21 CFR 601.2 (a) Applications for biologics licenses; procedures for filing, a BLA should contain “A full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide required under part 208 of this chapter proposed to be used for the product; and the address of each location involved in the manufacture of the biological product shall be listed in the biologics license application.” Furthermore, as defined in 21 CFR 600.3(t) “Manufacturer means any legal person or entity engaged in the manufacture of a product subject to license under the act; "Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards.”

We note that the table on page 8 of the briefing package indicates that a separate 3.2.S Module for the hP67.6 antibody will be submitted with the BLA. We agree with this, however, even if a determination is made that the submission should be an NDA, it would remain acceptable to include this module with information regarding the [b] [4] (b) [4] in the application.
2.0  DISCUSSION

The Sponsor submitted a slide presentation before the meeting to facilitate discussion which is attached to this meeting minutes.

**Question 1:**

Pfizer intends to apply the starting material strategy feedback received for ... Does the agency agree?

**FDA Response to Question 1:**

As discussed during the meeting with the sponsor on 14-Mar-2014 regarding ... as proposed starting materials will be determined during the review of the BLA application. We reserve the same comment for gemtuzumab ozogamicin. We recommend that the most appropriate starting material for...

Based on Guidance for Industry Q11 “Development and Manufacture of Drug Substances” you may apply a similar starting material strategy provided that you demonstrate that the fate and purge of impurities are adequately controlled. Your BLA should include manufacturing process description for ... beginning with previously approved starting materials, description of how impurities are formed in the process, how changes in the process could affect the impurity profile and why the proposed control strategy is suitable for the drug substance manufacturing process.

**Meeting Discussion**

Pfizer acknowledges the feedback provided and plans to provide the requested information in the BLA to support the proposed starting materials, ... . Pfizer would also like to understand the divergence in feedback for the proposed starting materials relative to the ... feedback. Pfizer thought the ... was accepted as a starting material contingent on sufficient information being provided in the registration dossier. The acceptability of ... as a starting material was agreed to be a review issue, and there was no premise of the ... being the most appropriate starting material.

The Agency explained that ... process is critical in controlling the impurity profile. Manufacturing steps that impact the impurity profile of the drug substance should be included in the manufacturing process and described in section 3.2.S.2.2 of the application.

Additionally, the source ... of the starting material could change without notification and affect the impurity profile in the drug substance and carry forward to the drug product. Since the control of impurities can impact your product, the Agency recommended that the ... be designated as the starting material.
Pfizer asked if there was any barrier to using the as the starting material. The Agency stated that the suitability of as a starting material, along with its specifications will be assessed at the time of the BLA review taking into consideration the overall assessment of CMC information provided in the BLA submission.

Question 2:
The gemtuzumab ozogamicin manufacturing process was validated prior to the original 1999 NDA submission in line with expectations and guidelines in place at the time. Subsequent changes were handled as post-approval changes and individually validated at the time of implementation. Pfizer intends to provide the most recent validation information for the respective components that spans from 1999 to 2014, and has not revalidated the overall gemtuzumab ozogamicin process for re-registration. The process has been validated and, in accordance with the validation results will be available during pre-approval inspection or upon formal request by the agency. Does the FDA agree Pfizer can proceed with registration using the proposed validation package?

FDA Response to Question 2:
The FDA does not agree with Pfizer’s proposed validation package with respect to the BLA submission. The sponsor notes in the meeting package, that the manufacturing process remains in a validated state. We request that Pfizer includes validation data of all components, including drug substance and drug product as part of the BLA submission.

Regarding your registration package should also include a detailed manufacturing description. The acceptability of the proposed starting material will be a BLA review issue. We emphasize that the most appropriate starting material for see Response to Question 1.

Meeting Discussion:
Pfizer plans to align the validation package with the proposed starting materials. Consistent with the feedback, Pfizer intends to provide manufacturing descriptions for the starting materials and information supporting the starting material selection in the BLA as requested in Question 1.

Validation information will be provided for:
- manufacture starting from the designated starting materials
- manufacture,
- Gemtuzumab ozogamicin drug substance manufacture,
- Gemtuzumab ozogamicin drug product manufacture
- Validation is not required for .

The and drug substance will be a compilation of historical validations comprised of the original validation and subsequent post approval changes.
and drug product validation information will consist of the most recent validation to support the current commercial site; validations for previous commercial sites will not be provided. Additionally, comparability data will be provided that is derived from a 2014 routine drug product manufacturing campaign to support the introduction of the proposed commercial production of [b] [4]. See Figure 1.

Pfizer plans to fully support the proposed starting materials in the BLA, and will provide information concerning the manufacturing processes of the proposed starting materials and the origin and fate of impurities during manufacturing. Understanding that the acceptability of the starting materials is a review issue, does the agency agree with this approach?

The Agency responded that there are different requirements between NDAs and BLAs regarding the submission of process validation information and is trying to find a balance specifically for gemtuzumab ozogamicin, since the sponsor likely has a validated process. Pfizer’s proposal as described may be acceptable.

The Agency asked when they plan to submit the BLA. The sponsor responded that they plan to submit in the first quarter of 2016 however it may be a little earlier.

**Question 3:**
Does the FDA agree that Pfizer can proceed with a submission using the proposed CMC package for gemtuzumab ozogamicin?

**FDA Response to Question 3:**
Overall, we agree with your approach to update the submission to the CTD format. We also agree that you should include a separate 3.2.S module regarding the manufacturing and characterization and validation of the [b] [4]. However, the acceptability of the package will be a BLA review issue.

**Meeting Discussion:**
Pfizer acknowledges the feedback.

**Additional FDA comments:**
Please address these comments in the BLA submission.

1. Your submission dated September 16, 2013 provided comparability data for gemtuzumab ozogamicin drug product manufactured at [b] [4] and at your facility in Pearl River, NY. We agree that lots manufactured at the Pearl River facility met the comparability acceptance criteria, but we note that there were differences between lots manufactured at the two sites with respect to (the mean at Pearl River was [b] [4]), the binding ELISA (the mean at Pearl River was [b] [4]) and cytotoxicity (the mean at Pearl River was [b] [4]). The Pearl River lots may have met stability criteria to support comparability, but results that are out of trend with the pre-change lots may be a concern. At the time we reviewed this submission however, it was not clear if the lots manufactured at Pearl River were derived from a limited number of [b] [4] lots and therefore, may not be representative of the variability of the drug substance and drug product lots when manufactured from multiple different lots of [b] [4].

Reference ID: 3683254
**Meeting Discussion:**

The Pearl River lots used the same ingoing material lot diversity as those produced from Two ingoing lots and 4 ingoing lots were used in manufacture of the three Pearl River lots. The noted differences in levels are attributed to the facility handling differences between and Pearl River. The Pearl River batches were conditions compared to the routine production process.

While the values were slightly higher than the previous validation criteria were met.

The 2014 production campaign was run employing engineering controls; the levels trend with previous values. These batches manufactured at Wyeth, Pearl River and represent the proposed commercial process. Information for these batches will be provided in the BLA.

The noted differences in binding ELISA and cytotoxicity are within the method variability and experience. Supportive information about the capability of these methods will be provided in the BLA.

Also of note, Pfizer has identified an error in the drug product specification on file. The correct specification for is μg/mg, with no separate release and stability specification. This will be corrected in the next amendment. This is also the acceptance criteria that were applied to the 2012 validation.

2. Your submission dated July 25, 2014 reports the characterization of a newly identified, but pre-existing . Provide information in the BLA regarding how you will control for the level of, either through in-process or release testing, and/or through process controls. The BLA should also contain the data provided in your July 25, 2014 submission demonstrating that the

**Meeting Discussion:**
Is this approach acceptable to the agency?

Pfizer stated that when the BLA is filed, they will have a qualified [REDACTED] assay. They will include supportive data on the method performance and they may pursue process monitoring control.

The Agency responded that this is reasonable and should be addressed in the BLA. There should be no safety concern associated with the process changes chosen [REDACTED].

3. Module 3.2.5 for the [REDACTED] gemtuzumab ozogamicin drug substance should contain the following product quality microbiology information:
   - Bioburden and endotoxin levels [REDACTED] should be monitored using qualified bioburden and endotoxin tests.

Meeting Discussion:

Rationale for the microbiological control strategy will be provided in the BLA.

Future batches will test both bioburden and endotoxin at critical steps.

- Microbial data from three successful [REDACTED] validation runs at manufacturing scale should be provided.

For drug substance, microbial control [REDACTED] were supported by both bioburden and endotoxin testing, [REDACTED] as requested.

Pfizer
plans to provide supplemental bioburden and endotoxin data from three batches collected during a routine 2014 production campaign. Bioburden and endotoxin monitoring will be implemented as routine monitoring for future batches.

- Data demonstrating microbial control

Pfizer also agrees to provide microbial control data for

Drug substance Data to support microbial control will be provided in the BLA.

- Bioburden and endotoxin data obtained during manufacture of the three process qualification batches (3.2.S.2.5).

As discussed above, the previously submitted and approved process qualifications for did not include endotoxin in all cases.

Supplemental bioburden and endotoxin data from recent 2014 routine production campaigns for and drug substance will also be provided.

- Summary of shipping validation studies and data (3.2.S.2.5).
- and gemtuzumab ozogamicin DS bioburden and endotoxin release specifications (3.2.S.4). The adequacy of the bioburden methods will be assessed during the BLA review.
- Summary report with summary results from bioburden and endotoxin test method qualification performed for drug substance (3.4.S.4).

Pfizer would like to confirm that bioburden and endotoxin methods used for have been appropriately qualified. Method details will be provided in the BLA.

4. The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”. Provide information and validation data summaries in Section 3.2.P.3.5 for the following:
Meeting Discussion:
The requested information will be provided in the BLA. Supplemental bioburden and endotoxin data from a 2014 routine production campaign will be provided in the BLA.

5. The following method validation information should be provided:
   - Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially to qualify the container closure system and process and during stability. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing be performed in lieu of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).
   - Qualification data for bioburden, sterility and endotoxin test methods performed for [redacted] where applicable) and the drug product, as appropriate (3.2.P.5).
   - Rabbit Pyrogen Test results from three lots of drug product in accordance with 21 CFR 610.13(b).

6. Inspection Readiness: All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the [redacted] drug substance and drug product fill finish sites should be included in Module 1 of the BLA. The facilities where [redacted] and the [redacted] are manufactured should also be ready for inspection.

Meeting Discussion:
Pfizer acknowledges the feedback. Manufacturing schedules will be provided for the [redacted] drug substance and drug product. [redacted] is
manufactured at Wyeth, Pearl River, NY, the same facility as drug substance and drug product, and will be inspection ready upon submission. The [b] site of manufacture will be provided in the BLA.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARJORIE A SHAPIRO
01/06/2015