CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761046Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>BLA #</th>
<th>761046</th>
<th>NDA Supplement #</th>
<th>N/A</th>
<th>BLA Supplement #</th>
<th>N/A</th>
<th>If NDA, Efficacy Supplement Type:</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(an action package is not required for SE8 or SE9 supplements)</td>
<td></td>
</tr>
<tr>
<td>Proprietary Name:</td>
<td>Zinplava</td>
<td>Applicant:</td>
<td>Merck Sharpe and Dohme, Corp.</td>
<td></td>
<td>Agent for Applicant (if applicable):</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Established/Proper Name:</td>
<td>Bezlotoxumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Division:</td>
<td>Division of Anti-Infective Products</td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>Injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RPM:</td>
<td>J. Christopher Davi, MS, Senior RPM, DAIP</td>
</tr>
<tr>
<td>BLA Application Type:</td>
<td>X 351(a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For ALL 505(b)(2) applications, two months prior to EVERY action:</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>• Review the information in the 505(b)(2) Assessment and submit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>the draft(^2) to CDER OND IO for clearance.</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□ No changes</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>□ New patent/exclusivity <em>(notify CDER OND IO)</em></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Date of check:</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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.

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\[\text{X AP} \quad \text{□ TA} \quad \text{□ CR}\]

\[\text{N/A}\]

\[\text{None}\]

\[\text{If not submitted, explain}\]

Review priority: ☐ Standard  X Priority
Chemical classification (new NDAs only):  N/A
(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
X REMS not required

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  Yes
- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action
    Yes
  - Indicate what types (if any) of information were issued
    FDA Press Release
- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    No
  - 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.
    N/A

## 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)*
  - Included: October 21, 2016

## 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: September 30, 2016
    - Included (PPI) October 6, 2016
  - Original applicant-proposed labeling
    - Included: November 23, 2015
    - Included (PPI) 11/23/15

- **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)*
    - None
  - Original applicant-proposed labeling
    - N/A

- **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

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
    - Granted (Zinplava)
    - Review: March 4, 2016
    - Letter: March 8, 2016

- **Labeling reviews** *(indicate dates of reviews)*
  - RPM: February 2, 2016
  - DMEPA: March 2, 2016
  - OPDP: September 22, 2016
  - Product Quality: June 3, 2016

## Administrative / Regulatory Documents

- **RPM Filing Review**/Memo of Filing Meeting *(indicate date of each review)*
  - Included: July 28, 2016
  - Not a (b)(2)

- **NDAs/NDA supplements only:** Exclusivity Summary *(signed by Division Director)*
  - N/A (BLA)

- **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
    - No
  - This application is on the AIP
    - N/A
    - 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
    - June 22, 2016

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4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
<table>
<thead>
<tr>
<th>Breakthrough Therapy Designation</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</td>
<td>N/A</td>
</tr>
<tr>
<td>- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)</td>
<td>N/A</td>
</tr>
<tr>
<td>- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)</td>
<td>N/A</td>
</tr>
<tr>
<td>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</td>
<td></td>
</tr>
</tbody>
</table>

- **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)*

- **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)

<table>
<thead>
<tr>
<th>Minutes of Meetings</th>
</tr>
</thead>
<tbody>
<tr>
<td>- If not the first review cycle, any end-of-review meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>- Pre-NDA/BLA meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>- EOP2 meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>- Mid-cycle Communication <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>- Late-cycle Meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>- Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <em>(indicate dates of mtgs)</em></td>
</tr>
</tbody>
</table>

- **Advisory Committee Meeting(s)**
  - **Date(s) of Meeting(s)**
    - Yes
    - June 9, 2016

## Decisional and Summary Memos

- **Office Director Decisional Memo** *(indicate date for each review)*
  - October 21, 2016
- **Division Director Summary Review** *(indicate date for each review)*
  - October 21, 2016
- **Cross-Discipline Team Leader Review** *(indicate date for each review)*
  - October 14, 2016
- **FMR/PMC Development Templates** *(indicate total number)*
  - Included (3)

## Clinical

- **Clinical Reviews**
  - **Clinical Team Leader Review(s)** *(indicate date for each review)*
    - See CDTL Memo
  - **Clinical review(s)** *(indicate date for each review)*
    - September 22, 2016
  - **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)*
    - Included in clinical review (pg. 124)
<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers</td>
<td>(indicate date of each review) None</td>
</tr>
<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation</td>
<td>(indicate date of each review) N/A</td>
</tr>
<tr>
<td>Risk Management</td>
<td>- REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</td>
</tr>
<tr>
<td></td>
<td>- REMS Memo(s) and letter(s) (indicate date(s))</td>
</tr>
<tr>
<td></td>
<td>- 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)</td>
</tr>
<tr>
<td>OSI Clinical Inspection Review Summary(ies)</td>
<td>(include copies of OSI letters to investigators) Included (May 12, 2016)</td>
</tr>
<tr>
<td><strong>Clinical Microbiology</strong></td>
<td>None</td>
</tr>
<tr>
<td>Clinical Microbiology Team Leader Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Clinical Microbiology Review(s) (indicate date for each review)</td>
<td>Included (May 2, 2016)</td>
</tr>
<tr>
<td><strong>Biostatistics</strong></td>
<td>None</td>
</tr>
<tr>
<td>Statistical Division Director Review(s) (indicate date for each review)</td>
<td>No separate review</td>
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<tr>
<td>Statistical Team Leader Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Statistical Review(s) (indicate date for each review)</td>
<td>May 12, 2016</td>
</tr>
<tr>
<td></td>
<td>Addendum: September 16, 2016</td>
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<tr>
<td><strong>Clinical Pharmacology</strong></td>
<td>None</td>
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<td>Clinical Pharmacology Division Director Review(s) (indicate date for each review)</td>
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<tr>
<td>Clinical Pharmacology Team Leader Review(s) (indicate date for each review)</td>
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<tr>
<td>Clinical Pharmacology review(s) (indicate date for each review)</td>
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<tr>
<td>OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)</td>
<td>None requested</td>
</tr>
<tr>
<td><strong>Nonclinical</strong></td>
<td>None</td>
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<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
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<td>ADP/T Review(s) (indicate date for each review)</td>
<td>No separate review</td>
</tr>
<tr>
<td>Supervisory Review(s) (indicate date for each review)</td>
<td>April 29, 2016</td>
</tr>
<tr>
<td>Pharm/tox review(s), including referenced IND reviews (indicate date for each review)</td>
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<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)</td>
<td>None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies (indicate date for each review)</td>
<td>No carc</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>None</td>
</tr>
<tr>
<td>OSI Nonclinical Inspection Review Summary (include copies of OSI letters)</td>
<td>None required</td>
</tr>
</tbody>
</table>

5 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).
## Product Quality

<table>
<thead>
<tr>
<th></th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Quality Discipline Reviews</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Tertiary review <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>• Secondary review (e.g., Branch Chief) <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <em>(indicate date for each review)</em></td>
<td>March 22, 2016 &amp; Addendum June 21, 2016</td>
</tr>
<tr>
<td><strong>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></strong></td>
<td>Product Quality/Micro (June 7, 2016)</td>
</tr>
<tr>
<td><strong>Environmental Assessment (check one) (original and supplemental applications)</strong></td>
<td></td>
</tr>
<tr>
<td>X Categorical Exclusion <em>(indicate review date)</em> (all original applications and all efficacy supplements that could increase the patient population)</td>
<td>Page 7 – Primary CMC Review (March 22, 2016)</td>
</tr>
<tr>
<td>□ Review &amp; FONSI <em>(indicate date of review)</em></td>
<td>N/A</td>
</tr>
<tr>
<td>□ Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td>In submission (Section 1.12.14)</td>
</tr>
<tr>
<td><strong>Facilities Review/Inspection</strong></td>
<td></td>
</tr>
<tr>
<td>X Facilities inspections <em>(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation)</em> (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

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<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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>For all 505(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td></td>
</tr>
<tr>
<td>• Finalize 505(b)(2) assessment</td>
<td>N/A</td>
</tr>
<tr>
<td>For Breakthrough Therapy (BT) Designated drugs:</td>
<td></td>
</tr>
<tr>
<td>• Notify the CDER BT Program Manager</td>
<td>N/A</td>
</tr>
<tr>
<td>For products that need to be added to the flush list (generally opioids): <strong>Flush List</strong></td>
<td></td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
<td>N/A</td>
</tr>
<tr>
<td>Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
<td>X Done</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>
<td>X Done</td>
</tr>
<tr>
<td>Ensure that proprietary name, if any, and established name are listed in the <strong>Application Product Names</strong> section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
<td>X Done</td>
</tr>
<tr>
<td>Ensure Pediatric Record is accurate</td>
<td>X Done</td>
</tr>
<tr>
<td>Send approval email within one business day to CDER-APPROVALS</td>
<td>X Done</td>
</tr>
</tbody>
</table>
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Regulatory Briefing
Meeting Date and Time: September 9, 2016; 11:00 AM-1:00 PM
Meeting Topic: BLA 761046 Zinplava (bezlotoxumab)
Meeting Chair: John K. Jenkins, M.D., Director, Office of New Drugs

PRESENTERS
Cheryl Dixon, PhD, Biostatistics Reviewer, Division of Biometrics IV
Shrimant Mishra, MD, Medical Reviewer, Division of Anti-Infective Products (DAIP)

Background:

Bezlotoxumab is a fully human monoclonal IgG1 antibody directed against C. difficile toxin B. The drug is proposed for prevention of C. difficile infection (CDI) recurrence in patients receiving standard of care (SOC) therapy for CDI. It is hypothesized that bezlotoxumab prevents binding of toxin B to colonic cells, thus averting colonic cell inflammation and preventing the development of CDI. Bezlotoxumab is administered as a single 10 mg/kg infusion at any time during CDI antibacterial therapy, which is usually 10-14 days in duration. The elimination half-life of bezlotoxumab is approximately 19 days. No drugs are currently approved for the prevention of CDI recurrence.

BLA 761046 for bezlotoxumab has been under review since November 2015. The BLA was presented at an advisory committee meeting in June 2016, and the review clock was extended by three months in July 2016. The extension was required to conduct additional analyses evaluating the potential negative impact of bezlotoxumab on cure of the initial episode of CDI and to gain further understanding of the benefit for patients in reduction of recurrence. During the review cycle, the Applicant (Merck) proposed a revised definition of the initial cure of CDI, which required additional review.

The presentation at the regulatory briefing focused on the discordant results of the two Phase 3 trials, limitations of the primary endpoint for these trials, and on the additional analyses conducted by the Division.
The panelists were asked to discuss whether the data are adequate to support the efficacy of bezlotoxumab for the prevention of CDI recurrence. Only a brief summary of the safety findings in the bezlotoxumab Phase 3 trials was included in the briefing document, as the safety profile of bezlotoxumab was considered acceptable and was not planned to be discussed in detail at the regulatory briefing.

**Discussion:**

- The Panel asked the presenter how long patients were followed for recurrence. The presenter confirmed this to be 90 days. The expanded definition for clinical cure can lessen the total follow-up per subject. It was noted that within a two week treatment period, there seemed to be a “de-minimis” difference between placebo and bezlotoxumab.

- The presenter clarified the difference between the original and “expanded” definitions of clinical cure, the former requiring less than or equal to 14 days of Standard of Care (SOC) where the later definition did not limit the duration of SOC. The median duration of SOC was 16 days. In the expanded definition, subjects who had any two (2) consecutive days of no loose stools were considered cured (but could “recur”).

- It was noted that the expanded definition (3 weeks) essentially allows for full follow-up for assessing recurrence (i.e., 9 weeks of follow-up). Based on the information presented in Slide 11, the presenter felt that bezlotoxumab does have an effect on recurrence, but there could also be an effect on initial clinical cure. It was asked if there would be an effect on Global cure. The Presenter indicated that it was believed that the results would be similar to CDI recurrence but that one would have to double check the numbers.

- With regard to slide #20, it was asked what the criteria were for receiving vancomycin over metronidazole. It was indicated that this was the choice of the clinician. For severe *C. difficile* colitis, it was noted that patients should not receive metronidazole. This is basically a surrogate of severity of the illness.

- With regard to fecal transplantation, the presenter was asked when this might be employed. In general, this was reserved for patients that have several recurrences and are not responding to traditional therapy. It was noted that fecal transplantation is not an approved therapy but can work fairly well at reducing recurrences. In Study P002, it was noted that 10 of the 20 fecal transplants were conducted at two sites, where all but 3 of the subjects with recurrences at these two sites received a fecal transplant.
- It was asked why the monoclonal antibody was administered during SOC rather than after the initial course of therapy. It was noted that many of the patients were outside of a hospital setting when they achieved initial cure. If one does not think that the monoclonal antibody would interfere with initial cure, it may just be that it is more convenient to administer it during the initial course of SOC. The presenter noted that part of the reason may be that the Sponsor wanted to mirror what would be done as part of clinical practice.

- It was noted that in some cases, some additional antibacterial therapy may have been necessary and loose stools may have continued for 1 to 2 additional days. However, in several analyses, there seems to be a reduction in recurrences and also that there might be evidence to support that the recurrences might be less severe. It was suggested that additional sensitivity analyses may help better define these issues, including analyses on the duration of hospital stays, etc., that may better inform the risk/benefit profile of the drug.

- Concern was expressed around the actual definition of recurrence, indicating that it was not particularly useful as defined. It should have been defined as a fraction of the patients who actually had a clinical cure. Failure of an initial cure (in this analysis) is being treated as a success, which is not particularly useful. Global cure would have been a much more useful endpoint. The panel discussed what the difference might be in terms of initial treatment with different comparators (vancomycin, fidaxomicin, etc.).

- The panel discussed what the population might be for which bezlotoxumab will be indicated. Sub-group analyses seem to indicate that the drug was not necessarily beneficial in particular subgroups. How the drug will be used is an important pharmaco-economic consideration. We do not want to treat patients that do not need to be treated at great economic cost.

- The Division was charged with labeling the product, if approved so that not every patient receiving an antimicrobial for CDI would receive this product.

-End
BLA 761046

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.  
Attention: Donnette D. Staas, PhD  
Director, Global Regulatory Affairs  
351 Sumneytown Pike  
UG2D-68  
North Wales, PA 19454-2504

Dear Dr. Staas:

Please refer to your Biologics License Application (BLA) dated November 17, 2015, received November 23, 2015, submitted under section 351(a) of the Public Health Service Act for Bezlotoxumab Injection, 25 mg/mL.

On June 30, 2016, we received your June 30, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 23, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 23, 2016.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker  
Chief, Project Management Staff  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research
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/s/

MAUREEN P DILLON PARKER
07/19/2016
BLA 761046

MID-CYCLE COMMUNICATION

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Donnette D. Staas, PhD
Director, Global Regulatory Affairs
351 Sumneytown Pike
UG2D-68
North Wales, PA 19454-2504

Dear Dr. Staas:

Please refer to your Biologics License Application (BLA) dated November 17, 2015, received November 23, 2015, submitted under section 351(a) of the Public Health Service Act for Bezlotoxumab Injection, 25 mg/mL (MK-6072).

We also refer to the teleconference between representatives of your firm and the FDA on March 22, 2016. The purpose of the teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Mid-Cycle Communication Minutes
Mid-Cycle Communication

Meeting Date and Time: March 22, 2016
Application Number: BLA 761046
Product Name: Bezlotoxumab (MK-6072)
Indication: CDI recurrence in patients 18 years and older
Applicant Name: Merck, Sharpe & Dohme, Corp.

Meeting Chair: Sumathi Nambiar, MD, MPH, Director
Division of Anti-Infective Products (DAIP)

Meeting Recorder: J. Christopher Davi, MS, Senior Project Manager, DAIP

FDA ATTENDEES: Division of Anti-Infective Products (DAIP)*
*Unless otherwise specified
John Farley, MD, MPH, Deputy Director, Office of Antimicrobial Products (OAP)
Sumathi Nambiar, MD, MPH, Director
Joseph Toerner, MD, MPH, Deputy Director for Safety
Dmitri Jarikov, MD, PhD, Clinical Team Leader
Hiwot Hiruy, MD, Clinical Reviewer
Karen Higgins, ScD, Biostatistics Team Leader
Cheryl Dixon, PhD, Biostatistics Reviewer
Jeff Florian, PhD, Pharmacometrics Team Leader
Luning (Ada) Zhuang, PhD, Pharmacometrics Reviewer
Seong Jang, PhD, Clinical Pharmacology Team Leader
Yang He, PhD, Clinical Pharmacology Reviewer
Kerian Grande-Roche, PhD, Clinical Microbiology Reviewer
Terry Miller, PhD, Non-Clinical Pharmacology Reviewer
Rashmi Rawat, PhD, Product Quality Team Leader, Office of Biopharmaceutics (OBP)
William Hallett, PhD, Product Quality Reviewer, OPB
Natalia Pripuzova, PhD, Product Quality/Microbiology Reviewer, OPQ
Colleen Thomas, PhD, Quality Assessment Leader, OPQ
Sevan Kolejian, PhD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Maureen Dillon-Parker, Chief Project Manager
J. Christopher Davi, MS, Senior Regulatory Project Manager
1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

We have concern regarding the evidence of efficacy of the product. As our assessment currently stands, Study 1 results are concerning due to the lower rate of initial cure as well as the failure to achieve significance in global cure for bezlotoxumab compared to placebo.
Additionally, Study 2 appears to have an imbalance in the number of subjects who had a new episode of diarrhea following clinical cure but whose stool was not collected for toxin testing. We continue to analyze the differing efficacy results in your two phase 3 trials and as of now, have been unable to understand what may be driving the findings.

**Post meeting note:** During the teleconference, the Sponsor indicated that they have conducted additional sensitivity analyses that may address the above referenced issue regarding the lower rate of initial cure in Study 1. As for the imbalance in the number of subjects without stool collected for toxin testing in Study 2, the Sponsor will provide additional information on such subjects including symptoms and any treatment received. The Division agreed to consider this information when submitted.

3.0 INFORMATION REQUESTS

We appreciate your replies to our information requests as the review of your BLA continues. The product quality information request of March 16, 2016, remains outstanding.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

As indicated in our filing communication letter dated February 5, 2016, your application will be the subject of an antimicrobial drug advisory committee meeting on June 9, 2016. This meeting will take place at the CDER White Oak Campus. We plan on providing the briefing document for the advisory committee meeting to you on May 18, 2016.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting for this application will be a face-to-face meeting and will be held on May 25, 2016, on the CDER White Oak campus. The briefing document for the advisory committee meeting referenced above will serve as the background material for this meeting. If we have additional items to discuss at the late-cycle meeting we will convey them to you in advance under separate cover.

-End
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/s/

JOSEPH C DAVI
04/04/2016

SUMATHI NAMBIAR
04/04/2016
Merck, Sharp & Dohme Corp, a subsidiary of Merck and Co.,Inc.
351 Sumneytown Pike
UG2D-68
North Wales, PA 19454-2504

ATTENTION: Donnette Staas, PhD
Director, Global Regulatory Affairs

Dear Dr. Staas:

Please refer to your Biologics License Application (BLA) dated November 22, 2015, received November 23, 2015, submitted under section 351(a) of the Public Health Service Act for Bezlotoxumab, 25 mg/ml.

We also refer to your correspondence, dated and received, January 6, 2016, requesting review of your proposed proprietary name, Zinplava.

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

If any of the proposed product characteristics as stated in your January 6, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5413. For any other information regarding this application, contact Chris Davi, Regulatory Project Manager in the Office of New Drugs, at 301-796-0702.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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/s/

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LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/08/2016
Dear Dr. Staas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-6072 (rINN bezlotoxumab) intravenous.

We also refer to the meeting between representatives of your firm and the FDA on September 29, 2015. The purpose of the meeting was to discuss the submission of a Biologic Licensing Application (BLA) for MK-6072.

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 J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s): Meeting Minutes
Division’s Preliminary Responses dated September 25, 2015
Sponsor’s slide presentation September 29, 2015
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: September 29, 2015
Meeting Location: CDER White Oak Campus
Application Number: IND 12,823
Product Name: MK-6072 (bezlotoxumab) intravenous
Indication: Clostridium difficile infection (CDI) recurrence
Sponsor/Applicant Name: Merck Sharp & Dohme Corp.

Meeting Chair: Sumathi Nambiar, MD, MPH Director
Meeting Recorder: J. Christopher Davi, MS, Senior Regulatory Project Manager

FDA ATTENDEES: Division of Anti-Infective Products (Division)*
*Unless otherwise noted
John Farley, MD, MPH, Deputy Director, Office of Antimicrobial Products
Sumathi Nambiar, MD, MPH, Division Director
Joseph Toerner, MD, MPH, Deputy Director for Safety
Dmitri Iarikov, MD, PhD, Medical Team Leader
Shrimant Mishra, MD, Medical Reviewer
Seong Jang, PharmD, Acting Clinical Pharmacology Team Leader
Yang He, PharmD, Clinical Pharmacology Reviewer
Rashmi Rawat, PhD, Product Quality Biology Team Leader, Office of Biotechnology (OBT)
Chikako Torigoe, PhD, Product Quality Biology Reviewer, OBT
Will Hallett, PhD, Product Quality Biology Reviewer, OBT
Kerry Snow, MS, Clinical Microbiology Team Leader
Kerian Grande Roche, PhD, Clinical Microbiology Reviewer
Wendelyn Schmidt, PhD, Non-Clinical Pharmacology Reviewer
Daphne Lin, PhD, Deputy Director, Division of Biometrics IV
Karen Higgins, ScD, Biostatistics Team Leader
Cheryl Dixon, PhD, Biostatistics Reviewer
Maureen Dillon-Parker, Chief, Project Management Staff
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES: Merck Sharp & Dohme Corp.
Mary Beth Dorr, PhD, Director, Clinical Research
Dalya Guris, MD, MPH, Executive Director, Clinical Research
Nicholas Kartsonis, MD, Associate Vice President, Clinical Research

Reference ID: 3834926
BACKGROUND:

Merck Sharp & Dohme Corp. (Sponsor) requested a Type-B, Pre-BLA meeting, to discuss the submission of a marketing application for MK-6072 (bezlotoxumab) intravenous. The Division of Anti-Infective Products (Division) granted the meeting on July 31, 2015, and provided preliminary responses to the questions in the Sponsor’s briefing package on September 25, 2015 (appended). Discussion points generated from the preliminary responses are provided herein.

DISCUSSION

- The Sponsor opened the discussion, informing the Division that they were in agreement with the responses (appended) for questions 1, 3, 5, 7, 9 and 10. The Sponsor wished to focus the discussion on responses for questions 2, 4 and 8.

- The Sponsor provided a slide presentation (appended) showing a synopsis of the results of their phase 3 trials, and discussed primary and secondary efficacy results including various sub-group analyses.

- The Division informed the Sponsor that their approach for the extension of shelf-life for the product is reasonable, and that the data supporting this could be provided in the annual report.

- The Division acknowledged the points made in the Sponsor’s slide presentation. The Division reiterated that the difference in rate of initial cure is very important in assessment of the efficacy of MK-6072 in reduction of CDI recurrence. The Sponsor acknowledged this, indicating that they would include several sensitivity analyses in the application that would help to address this issue.

- The Division asked the Sponsor about possible explanations for seemingly worse efficacy outcomes associated with the use of anti-toxin A antibody. The Sponsor indicated that it is unclear why the administration of anti-toxin A antibody resulted in worse outcomes.
The Sponsor stated that the Division’s guidance on the combination rule led them to a better program with the ability to choose the product driving the effect, which was anti-toxin B only.

- The Division asked the Sponsor about the increase in deaths observed for the anti-toxin A arm at the interim analysis. The Sponsor indicated that study deaths were greater in the anti-toxin A arm, but that they did not feel that there was any indication that the deaths were occurring in any particular type of patient, or that deaths were conclusively attributed to study drug. The Sponsor stated that they will provide the interim analysis report, as well as the final data for the anti-toxin A arm.

- The Division and Sponsor discussed whether differences in patient demographics between the two trials may have contributed to some differences in efficacy outcomes observed in the trials. The Sponsor indicated that patient populations in the two phase 3 trials were similar overall, although the second trial had a larger Asian population and fewer US subjects (i.e., populations were slightly different but baseline characteristics were consistent across the trials).

- The Sponsor indicated that the intent of the development program was to be as inclusive as possible and that they allowed patients who had multiple recurrences to be enrolled. Approximately 15% had three or more previous episodes. The Sponsor felt that the enrollment profile in the trials mirrored what could be considered a relevant patient population in the clinical setting.

- The Division asked the Sponsor if they captured data on what the patient had received as standard-of-care (SOC) for previous episodes prior to enrollment. The Sponsor indicated that they captured this data (up to 30-days prior to enrollment) but not for episodes prior to 30 days.

- The Division asked the Sponsor if they (Sponsor) would provide case report forms (CRFs) for all discontinuations. Additionally, the Division asked for concise narratives to accompany the CRFs (if possible) and also informed the Sponsor that a request would be forthcoming for a 10% random sample of CRFs prior to BLA submission. The Sponsor will send to the Division, as soon as possible, patient ID numbers and treatment assignments so that the 10% sample can be generated. The Division inquired about obtaining narratives for all Serious Adverse Events (SAEs), however the Sponsor felt that this might be too difficult given the number of SAEs but agreed to provide the CRFs for such events. The Sponsor agreed to provide CRFs for all SAEs, discontinuations, deaths, as well as the 10% sample. Narratives will be provided for deaths, discontinuations, and any drug-related SAEs.

- The Sponsor informed the Division that in general, labs were not measured beyond a month unless a patient came in with recurrent diarrhea. However, immunogenicity testing was performed out to 90 days.
• The Division informed the Sponsor that their BLA would be reviewed under the PDUFA V “Program” and as such, all agreements for any components of the submission that may arrive after submission (e.g., within 30 days) would need to be made during the Pre-BLA meeting.

• The Sponsor indicated that with the exception of the stability update to be provided within 30 days of the submission, they planned on submitting a complete package in mid-November of 2015. The Division and Sponsor agreed that this was acceptable.

-End

ATTACHMENTS AND HANDOUTS:

Division’s Preliminary Responses dated September 25, 2015
Sponsor’s slide presentation September 29, 2015
Dear Dr. Staas:

In anticipation of our September 29, 2015, meeting the Division of Anti-Infective Products (DAIP) has reviewed your briefing document dated August 27, 2015, and we have the following preliminary responses (italics) to the questions you have asked:

**Question 1:** The Sponsor is requesting that the Agency confirm the feedback received during development of MK-3415A indicating that no additional toxicology studies are needed.

*Division Response: No additional toxicology studies are needed.*

**Question 2:** Does the Agency concur with the proposed list of comparability protocols to be submitted with the BLA, to support evaluation and reporting of intended post-approval changes?

*Division Response: It is unclear why you are proposing a comparability protocol. We generally do not require a comparability protocol in the BLA.*
**Question 3:** Does the Agency agree that a simple stability update can be filed within 30 days of the original BLA submission, to support drug substance and drug product shelf life assignment?

**Division Response:** Yes. Please note that "simple stability updates" are defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the "simple stability update" will use the same tabular presentation as in the original submission, as well as the same mathematical or statistical analysis methods (if any), and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA.

**Question 4:** Does the Agency agree that the efficacy and safety data from the pivotal Phase 3 trials (PN001 and PN002) are adequate to support a BLA submission for MK-6072 for the proposed indication for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI?

**Division Response:** The efficacy and safety data from both the pivotal Phase 3 trials along with information from the Phase 2 trials will support submission of the BLA. Based on the summary of the information submitted in the briefing package, we do have concerns regarding the results of the pivotal trials. We note the decreased initial clinical cure rates observed for the monoclonal antibodies as compared to placebo (both monoclonal antibodies in PN001 and the MK-3415A arm in PN002). Per our correspondence dated 8/21/13, we noted that our interpretation of the trials would depend on the number of subjects with clinical cure of the initial infection and if the monoclonal antibody arm had a lower initial cure rate than the placebo arm, then the interpretation of the CDI recurrence endpoint may be difficult. Whether or not these studies will be sufficient for approval will be a review issue.

To aid our interpretation of the study results, we request that you provide subgroup analyses similar to those presented in Tables 12 and 15 in the briefing package for the initial clinical cure endpoint as well as the global cure endpoint.

**Question 5:** Does the Agency agree that the Sponsor's proposed PK and exposure-response modeling approach is adequate to support review of the MK-6072 BLA?

**Division Response:** Your plans to apply modeling and simulation approach to support review of the MK-6072 BLA [i.e., development of a population PK model and an efficacy exposure-response analysis in CDI patients from the two pivotal Phase 3 trials (PN001 and PN002)] appear acceptable. However, whether the modeling and simulation results will be adequate to support registration of MK-6072 will be determined upon review. In order to facilitate the BLA review, we recommend that you include details of the population PK modeling and exposure-response results in Module 5 in your BLA submission, including base and final population PK model control streams (.txt files), exposure-response modeling scripts, and datasets (.xpt format) for the analyses.
Question 6: Does the Agency agree that the MK-6072 BLA will meet the criteria for a priority review?

Division Response: A determination on the review status of your application (i.e., Priority versus Standard) will be assessed at the time of BLA submission and you will be notified of the review designation.

Question 7: Does the Agency agree with the Sponsor’s request, on the basis that all trials are clinically complete and that all of the safety data for subjects who have received a dose of MK-6072, MK-3415 or MK-3415A will be included in the initial BLA, to waive the requirement for a Safety Update Report?

Division Response: Yes, this is acceptable.

Question 8: Does the Agency agree with the proposed content and format of the BLA as described in the Table of Contents, including the plans for integrated analysis of data from the clinical trials supporting safety and efficacy?

Division Response: In general your proposal is acceptable. In addition, please provide narratives for all discontinuations in the phase 2 and 3 trials. Please discuss whether any safety information (e.g., labs, nonserious AEs, etc.) were collected beyond the four week time point. This would be useful given the long half-life of the drug. Please clarify your plan for submission of case report forms (CRFs) in the BLA. Please also provide an integrated summary of microbiology and an index to the location of key microbiology studies and study reports that you will provide in the submission.

Question 9: Does the Agency agree that the content and presentation of the clinical pharmacology program will be adequate to allow review of the BLA in support of the application, without the need for a separate Clinical Pharmacology and Biopharmaceutics Review Aid?

Division Response: Yes, we agree.

Question 10: Does the Agency agree with the Sponsor’s proposed format for submission of summary level clinical site data sets to aid CDER’s Office of Scientific Investigations (OSI) data integrity review and inspection planning?

Division Response: The Agency concurs with this approach as outlined in your briefing document.
Additional Comments:

**Product Quality Microbiology:**

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Bioburden samples should be collected prior to any [redacted] step. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Bioburden samples should be collected prior to any [redacted] step.
- Storage validation data and information (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the PPQ batches (3.2.S.2.5).
- Summary of shipping validation studies and data (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed (3.4.S.4).
- The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the [redacted] 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 study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. The equipment requalification program should be described.
- [redacted] microbial controls and hold times. Hold times should be validated at manufacturing scale.
- Isolator decontamination, if applicable.
• Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
• A description of the routine environmental monitoring program.
• Summary of shipping validation studies and data.

The following method validation information should be provided:

• Container closure integrity testing (3.2.P.2.5). Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that 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 in-process intermediates and buffers (where applicable) and the drug product, as appropriate (3.2.P.5).
• Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610.13(b).
• The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

**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 bulk drug substance and drug product fill finish sites should be included in Module 1 of the BLA under section 1.3.

**ADDITIONAL APPLICATION INFORMATION - CONTENT OF A COMPLETE APPLICATION:**

As stated in our 07/31/15 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions.
You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application.

These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at:


**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:


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:  


**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

**MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.
Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

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<th>Site Name</th>
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<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
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<th>Onsite Contact (Person, Title)</th>
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We can discuss the above information with you in more detail at the September 29, 2015, meeting. If you have questions in the interim, I can be reached at (301) 796-0702.

J. Christopher Davi, MS
Senior RPM, DAIP

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

/s/

SUMATHI NAMBIAR
10/19/2015
LATE-CYCLE COMMUNICATION DOCUMENTS
Dear Dr. Staas:

Please refer to your Biologics License Application (BLA) dated November 17, 2015, received November 23, 2015, submitted under section 351(a) of the Public Health Service Act for Bezlotoxumab Injection, 25 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on May 25, 2016.

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

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-796-0702.

Sincerely,

{See appended electronic signature page}

Dmitri Iarikov, MD, PhD
Cross Discipline Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Late Cycle Meeting Minutes
Late Cycle Briefing Document dated May 20, 2016
Sponsor’s Slide Presentation
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: May 25, 2016
Meeting Location: CDER White Oak Campus

Application Number: BLA 761046
Product Name: Zinplava (bezlotoxumab) Injection
Indication: Clostridium difficile infection (CDI) recurrence
Applicant Name: Merck Sharpe & Dohme Corp., a subsidiary of Merck & Co., Inc.

Meeting Chair: Sumathi Nambiar, MD, MPH, Director, Division of Anti-Infective Products (DAIP)
Meeting Recorder: J. Christopher Davi, MS, Senior Regulatory Project Manager

FDA ATTENDEES: Division of Anti-Infective Products (DAIP)*:
*Unless otherwise specified
John Farley, MD, MPH, Deputy Director, Office of Antimicrobial Products (OAP)
Sumathi Nambiar, MD, MPH, Director
Joseph Toerner, MD, MPH, Deputy Director for Safety
Dmitri Iarikov, MD, PhD, Clinical Team Leader & Cross Discipline Team Leader
Shrimant Mishra, MD, Clinical Reviewer
Hiwot Hiruy, MD, PhD, Clinical Reviewer
Karen Higgins, ScD, Biostatistics Team Leader
Cheryl Dixon, PhD, Biostatistics Reviewer
Seong Jang, PhD, Clinical Pharmacology Team Leader
Yang He, PhD, Clinical Pharmacology Reviewer
Kerian Grande-Roche, PhD, Clinical Microbiology Reviewer
Terry Miller, PhD, Non-Clinical Pharmacology Reviewer
Rashmi Rawat, PhD, Product Quality Team Leader, Office of Biopharmaceutics (OBP)
Maureen Dillon-Parker, Chief Project Manager
J. Christopher Davi, MS, Senior Regulatory Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sese, Independent Assessor
Peggah Khorrami, Independent Assessor

Reference ID: 3949843
1.0 BACKGROUND

The Division of Anti-Infective Products provided a late cycle briefing package to the Sponsor on May 20, 2016 (appended). The Sponsor provided a slide presentation in response to the two substantive review issues identified (appended) in the briefing document. Discussion points generated from the slide presentation are recorded herein.

2.0 DISCUSSION

1. Discussion of Substantive Review Issues

Discussion:

- The Sponsor provided a slide presentation to address the two substantive review issues identified (appended). The Sponsor acknowledged that both endpoints (global cure and CDI recurrence) are affected by the clinical cure definition. The Sponsor indicated that they felt that an expanded definition of clinical cure, not requiring a pre-defined duration of Standard of Care (SOC) would be more appropriate to assess initial cure rates. When the expanded definition of clinical cure was used, there was no difference in cure rates between treatment groups. The Sponsor felt that bezlotoxumab did not have negative impact on clinical cure.

- The Division maintained that it is unclear how to interpret the results of the trials, because of the imbalances in initial cure rates. The Division indicated that in terms of clinical cure, the combination arm performed consistently worse than the placebo arm and it is not clear if this is being driven by anti-toxin A or anti-toxin B.
The Sponsor acknowledged this but felt that the presence of actoxumab in the combination arms suggested that bezlotoxumab was not the reason for the differences seen with clinical cure.

- The Division reiterated that the mechanism of action of bezlotoxumab is not fully understood, so it is not unreasonable to think that bezlotoxumab could have a negative impact on clinical cure.

- The Division indicated that imbalances in clinical cure warrant further discussion. The Sponsor indicated that they had enrolled a broad array of patients and that this had impacted how SOC was prescribed. Patients at high risk for recurrences (e.g., those receiving concomitant antibacterial drugs, oncology patients, and patients with multiple recurrences) could have received a longer duration of initial treatment per discretion of the investigator.

- The Division asked the Sponsor if they evaluated factors predictive of clinical failure, for instance the severity of the initial CDI. The Sponsor indicated that a high Horne’s index, low albumin level, and enrollment in North American clinical sites were predictors of clinical failure. The Sponsor indicated that they would look into more of the baseline characteristics to help further clarify this.

- With regard to a greater number of serious adverse events (SAE) of congestive heart failure (CHF) that occurred in subjects treated with the monoclonal antibodies as compared to placebo, the Sponsor indicated that the subjects with the SAE of CHF were elderly and had cardiac, as well as other underlying comorbidities. The Sponsor did not believe that there was a cardiac safety signal in association with bezlotoxumab. The Division acknowledged this but pointed out that demographic characteristics were balanced between the treatment arms and may not fully explain the imbalance in SAE related to CHF between the treatment arms.

- The Division asked the Sponsor about the timing of therapy, and when they felt it was optimal to administer bezlotoxumab. The Sponsor indicated that they envisioned administration of bezlotoxumab at any time during SOC therapy. They felt it shouldn’t be given after completing SOC therapy, since the at-risk period starts immediately following completion of SOC therapy. In addition, the Sponsor indicated that it may be challenging to administer bezlotoxumab upon completion of SOC therapy because the majority of patients would be treated in the outpatient setting at that time.
2. Review Plans

- The Division will continue the review process and make any necessary edits to the product label, which we may share with the applicant approximately 4 to 6 weeks prior to the action date. Tentative labeling discussions are scheduled as follows:
  - July 8, 2016
  - July 15, 2016

3. **Wrap-up and Action Items:** Minutes for this meeting will be issued by June 24, 2016.

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

-End
Dear Dr. Staas:

Please refer to your Biologics License Application (BLA) dated November 17, 2015, received November 23, 2015, submitted under section 351(a) of the Public Health Service Act for Bezlotoxumab Injection, 25 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 25, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Late-Cycle Meeting Background Package
LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: May 25, 2016
Meeting Location: CDER White Oak Campus

Application Number: BLA 761046
Product Name: Zinplava (bezlotoxumab) injection
Indication: Clostridium difficile infection (CDI) recurrence
Applicant Name: Merck Sharpe & Dohme Corp., a subsidiary of Merck & Co., Inc.

FDA ATTENDEES -Division of Anti-Infective Products (DAIP)*:
*Unless otherwise specified
Edward M. Cox, MD, MPH, Office Director, Office of Antimicrobial Products (OAP)
John Farley, MD, MPH, Deputy Director, OAP
Katherine Schumann, MS, Associate Director for Regulatory Affairs (OAP)
Sumathi Nambiar, MD, MPH, Director
Joseph Toerner, MD, MPH, Deputy Director for Safety
Dmitri Iarikov, MD, PhD, Clinical Team Leader
Shrimant Mishra, MD, Clinical Reviewer
Hiwot Hiruy, MD, Clinical Reviewer
Karen Higgins, ScD, Biostatistics Team Leader
Cheryl Dixon, PhD, Biostatistics Reviewer
Seong Jang, PhD, Clinical Pharmacology Team Leader
Yang He, PhD, Clinical Pharmacology Reviewer
Kerian Grande Roche, PhD, Clinical Microbiology Reviewer
Terry Miller, PhD, Non-Clinical Pharmacology Reviewer
Rashmi Rawat, PhD, Product Quality Team Leader, Office of Biopharmaceutics (OBP)
William Hallett, PhD, Product Quality Reviewer, OPQ
Natalia Pripuzova, PhD, Product Quality/Microbiology Reviewer, OPQ
Colleen Thomas, PhD, Quality Assessment Leader, OPQ
Sevan Kolejian, PhD, Safety Evaluator, Division of Medication Error Prevention and Analysis
Maureen Dillon-Parker, Chief Project Manager
J. Christopher Davi, MS, Senior Regulatory Project Manager

APPLICANT ATTENDEES: Merck Sharp & Dohme Corp.
Mary Beth Dorr, PhD, Director, Clinical Research
Yoshihiko Murata, MD, PhD, Director, Clinical Research
Dalya Guris, MD, MPH, Executive Director, Clinical Research
Nicholas Kartsonis, MD, Associate Vice President, Clinical Research
Randolph Matthews, MD, PhD, Principal Scientist, Translational Pharmacology
Alison Pedley, PhD, Principal Scientist, Clinical Biostatistics
Kenneth Koury, PhD, Executive Director, Clinical Biostatistics
Stefan Zajic, PhD, Principal Scientist, PK, PD and Drug Metabolism

Reference ID: 3949843
INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE:

1. **Discipline Review Letters:** No Discipline Review Letters have been issued to date.

2. **Discussion of Substantive Review Issues:**
   
   The following substantive review issues have been identified to date:
   
   a. We continue to investigate the varied efficacy findings between the two phase 3 trials. Specifically, we remain focused on what is the appropriate primary endpoint for both trials, discrepancies in clinical cure between the two trials, and whether substantial evidence of efficacy has been demonstrated.
   
   b. We have noted that more subjects in the bezlotoxumab (n=17) and actoxumab plus bezlotoxumab (n=17) arm who experienced congestive heart failure as a severe adverse event compared to those treated with placebo (n=7). In addition, subgroup analysis of subjects with baseline congestive heart failure showed that there were numerically higher proportion of severe adverse events and deaths in the bezlotoxumab-treated subjects compared to placebo. We continue to investigate these findings.
ADVISORY COMMITTEE MEETING

Date of AC meeting: June 9, 2016

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: May 18, 2016

Potential questions and discussion topics for AC Meeting are as follows:

Has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence?

- If yes, please provide any recommendations concerning labeling.
- If no, what additional studies/analyses are needed?

We discuss our plans for the presentations of the data and issues for the upcoming AC meeting below. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA:

1. **Introductory Comments**: Welcome, Introductions, Objectives of the meeting

2. **Information Requests**: We appreciate your prompt response to our information requests during the review cycle. A partial response to the following information request was received on March 16, 2016.

   Provide a complete list of diagnostic test methods used for the detection of toxigenic *Clostridium difficile* during Phase 3 clinical trials. Include the manufacturer’s package insert for each test method, and specify whether the test method is FDA cleared. If the test is not FDA cleared, then submit the complete assay validation/verification study report.

   The product insert/validation report for the non-FDA approved assays (\(\overset{\text{(a)}}{\text{(b)}}\text{ (4)}\)) is outstanding.
3. **Discussion of Upcoming Advisory Committee Meeting:** As noted above, the main topic of discussion from an efficacy standpoint will be the assessment of clinical outcomes in the two trials, including a discussion of the appropriate endpoint and the differences in the results between the two trials. From a safety standpoint, we expect there might be some discussion about the subgroup of patients with congestive heart failure. We also anticipate that there might be some discussions about the role of each of the antibodies and the interpretation of the clinical outcomes/recurrences when the antibodies are used alone or in combination.

4. **Review Plans:** We will continue the review process and make any necessary edits to a proposed version of the product label, which we may share with you approximately 4 to 6 weeks prior to the action date of July 23, 2016. Tentative labeling discussions are scheduled as follows:
   - July 8, 2016
   - July 15, 2016

5. **Product Quality Microbiology/CMC Related Post Marketing Commitments (PMCs):** It has been determined by the Product Quality Review team that the following PMCs apply to this application:
   - PMC #1: Re-evaluate MK-6072 DS and DP lot release and stability specifications after a minimum of 30 DS lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.
   - PMC #2: Perform additional testing to support the clonality of the bezlotoxumab master cell bank (MCB).
   - PMC #3: Conduct a study to support the worst case cumulative hold times in the bezlotoxumab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of bezlotoxumab drug substance. These data are expected to demonstrate that there is no adverse impact to product quality.
6. **Wrap-up and Action Items**: Minutes to be issued for this meeting within 30 days.

-End

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

/s/

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JOSEPH C DAVI
06/22/2016

DMITRI IARIKOV
06/22/2016