# Mid-Cycle Meeting Agenda/Summary

**Application number:** BLA 125661.0
**Product name:** JIVI (Recombinant B-domain deleted human coagulation factor VIII conjugated with polyethylene glycol (PEG) (BAY 94-9027))
**Proposed Indication:** Control and prevention of bleeding episodes and for surgical & long term prophylaxis in patients with hemophilia A
**Applicant:** Bayer Healthcare, LLC
**Meeting date & time:** February 12, 2018 [1:00pm – 2:00pm]
**Committee Chair:** Zuben Sauna
**Meeting Recorder:** Olukayode Owosela
Candace Jarvis

**Attendees:**

| Discipline | Name [with credentials (not title)] | Attended meeting? |
|---|---|---|
| Regulatory Project Manager (RPM) | Candace Jarvis<br>Olukayode Owosela | X<br>X |
| Chair/ CMC Inspector | Zuben Sauna | X |
| Clinical Reviewer | Megha Kaushal | X |
| CMC Reviewer | Ze Peng<br>Daniel Lagasse | <br>X |
| Clinical Pharmacology Reviewer | Iftekhar Mahmood | X |
| Toxicology Reviewer | Sandhya Sanduja | X |
| OCBQ/DMPQ RPM | Ekaterina Allen | X |
| OCBQ/DMPQ Reviewer | Lori Peters | X |
| OCBQ/DMPQ/PRB Reviewer | Cheryl Hulme | |
| Statistical Reviewer of clinical data | Lin Huo | X |
| Post marketing Safety Epidemiological Reviewer | Graca Dores | X |
| OCBQ/APLB Reviewer | Kristine Khuc | X |
| OCBQ/BIMO Reviewer | Bhanu Kannan | X |
| OCBQ/DBSQC RPM | Varsha Garnepudi | X |
| OCBQ/DBSQC or OVRR/LIB Reviewer | Hyesuk Kong<br>Parmesh Dutt<br>Ritu Agarwal<br>Hsiaoling Wang<br>Lokesh Bhattacharyya (Supervisor) | X<br>X<br>X<br>X |
| OCBQ/DMPQ/Lead Inspector | Lori Peters | X |
| Labeling Reviewer | Oluchi Elekwachi | |

| | | |
|---|---|---|
| Other Attendees | Ramani Sista | X |
| | Kimberly Benton | X |
| | Rachael Anatol | |
| | Wilson Bryan | X |
| | Timothy Lee | X |
| **Discipline** | **Name [with credentials (not title)]** | **Attended meeting?** |
| | Basil Golding | |
| | Mahmood Farshid | X |
| | Patrick Riggins | X |
| | Carolyn Renshaw | |
| | John Eltermann | X |
| | Lisa Stockbridge | |
| | Mercedes Serabian | X |
| | Iwen Wu | X |
| | Deborah Trout | X |
| | Ilan Irony | |
| | Tejashri Purohit-Sheth | |
| | Bindu George | |
| | Renee Rees | |
| | Larissa Lapteva | |

**Discussion Summary:**

This meeting is to discuss the review status of BLA 125661. We will discuss any outstanding review issues as well and determine the agenda for the Mid-Cycle communication

**Report and Discuss:**

1. Reviewer Reports

    a. Zuben Sauna, Daniel Lagasse, and Ze Peng - **CMC**
        i. Substantive issues to report
            1. None
        ii. One pending IR response due Feb. 16
        iii. IR to be sent out soon (Ze Peng)

    b. Hyesuk Kong, Parmesh Dutt, Ritu Agarwal, Varsha Garnepudi, and Hsiaoling Wang – **DBSQC**
        i. Substantive issues

1. The method validation for the following assays is incomplete. The deficiencies are being communicated through second IR.

   (b) (4) Drug Product
   - Purity by (b) (4)
   - Quantitation of Histidine and Glycine by (b) (4)
   - Determination of Polysorbate 80 by (b) (4) method
   - Quantitation of Sodium and Calcium by (b) (4) (requires re-validation using product in this submission)
   - Determination of (b) (4) o (requires re-validation using product in this submission)

   Drug Product
   - Determination of Color and clarity
     (Requires Validation as per ICH (Q2) R1 guidelines- Instrument performance data using appropriate reference standard and precision data
   - Determination of Particulate Matter
     (Requires Validation as per ICH (Q2) R1 guidelines- Instrument performance data using appropriate reference standard and precision data
2. Moisture determination: incorrect calculation formula in the method.
3. Chromatography assay for (b) (4) : Insufficient validation

ii. Pending IR from Nov. 17, 2017 and Jan. 23, 2018
iii. IR to be sent out (Ritu Agarwal) regarding item i.
iv. IRs regarding potency assays may be sent out if deemed necessary

c. Lori Peters – **DMPQ**
   i. Substantive issues
      1. None
   ii. IR to be sent out toward the end of February.

d. Sandhya Sanduja – **Pharmacology/Toxicology**
   i. Substantive issues
      Ongoing Issue - A 26-week IV toxicity study in immune-deficient (b) (4) nude male rats, with a 26-week recovery interval, is ongoing. This study was requested by FDA in the May 31, 2017 Type B pre-BLA meeting. The applicant plans to submit an audited interim report containing all in-life data from all study animals and post-mortem data (including histopathology) from the animals sacrificed at the weeks 13 and 26 time points, in an amendment to

the BLA by April 30, 2018, and a final audited report (to also include the 26-week recovery data) in the first quarter of 2019. The contents of the study report and possibly the date that the amendment is submitted will determine if it will constitute a Major Amendment to the BLA.

e. Megha Kaushal – **Clinical**
    i. Substantive issues
        1. Issues can be addressed by labeling and do not affect approval
    ii. IRs to be sent out

f. Iftekhar Mahmood – **Clinical Pharmacology**
    i. Substantive issues
        1. None
    ii. No pending IRs

g. Lin Huo – **Biostatistics**
    i. Substantive issues
        1. The only pivotal study PROTECT VIII (in adults and adolescents) was reviewed and the primary efficacy results are as follows:
            a. **Part A** During the 26-week treatment period, the median ABR was 2.09 when all prophylaxis groups were combined compared to an ABR of 23.42 in the on-demand group. By regimen, median ABRs were 4.11 and 1.93 in the 2x/week failed and forced groups, respectively, 1.93 in the every 5-day, and 3.85 in the every 7-day groups.
            b. **Part A Extension** The median ABR was 1.17 when all prophylaxis groups were combined compared to an ABR of 32.96 in the on-demand group. By regimen, median ABRs were 2.21 in the 2x/week group, 1.17 in the every 5-day, 0.54 in the every 7-day, and 3.94 for patients with “variable frequency” groups.
            c. **Part B and extension** JIVI was used for hemostatic control in a total of 20 major surgeries in 17 patients. Fourteen were orthopedic joint surgeries. Treatment with JIVI provided “good” or “excellent” hemostatic control during all major surgeries. IR to be sent out
    ii. IR to be sent out regarding 3 bleeding events detected after database lock

h. Kristine Khuc – **APLB**

i. Suffix Letter-ready comments to be provided to RPMS to send in IR/Advice.
ii. *Update- Bayer has submitted proposed suffixes for their proper name. IR not needed.

i. Bhanu Kannan – **BIMO**
   i. Substantive issues
      1. None
   ii. 2 of the 4 inspections completed

j. Graca Dores – **Epidemiology**
   i. Substantive issues
      1. Potential long term PEG-related adverse reactions - awaiting results of the 26-week pre-clinical study on immune deficient (b) (4) nude male rats. This information is required to finalize the pharmacovigilance plan.
      2. Other notable clinical events will need to be addressed through the PVP and/or other mechanisms (e.g., labeling).
   ii. IRs will be sent out on some of submitted materials. DE cannot address all elements requiring further follow-up in the PVP without the results of the pre-clinical long-term toxicity study being available for review, as noted above.

2. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation. ***[Review Committee Members]***

   The need for the advisory committee will be determined upon submission of the preclinical data expected end of April.

3. Determine whether Post Marketing Requirements (PMRs), Post marketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed. **[C*linical Reviewer, Chair]***

   *i. Will there be a Title IX PMR requiring SWG review?*

   *ii. If the determination is made that a PMC or PMR is needed, begin the development of the language for the approval letter.*

   This information is also contingent on the preclinical data expected at the end of April.

4. National Drug Code (NDC) assignments to product/packaging (excludes devices).

The NDCs are being reviewed and verified for the carton, sample cartons and vials.

5. Proper naming convention.

   The proper name for this product is Antihemophilic Factor (Recombinant), PEGylated. The proprietary name is JIVI.

6. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

   DMPQ - ***Lori Peters --*** Facility inspections for this BLA have been waived; waivers are included in the EDR for this BLA

   Main facility is being waived; 2 Diluent facilities have good history and are also being waived.

   BIMO- ***Bhanu Kannan***

| **Site #** | **Number of subjects** | **Location** | **Inspection Status** |
|---|---|---|---|
| 14002 | 10 | Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania | Completed as of the meeting. No 483. Pending review of the report |
| 14013 | 3 | SUNY Upstate Medical University Syracuse, New York | No 483, Pending review of the report |
| 14024 | 3 | University of California -Davis | Inspection pending. |
| | | Sacramento, California | |
| 68001 | 6 | Singapore General Hospital, Singapore | No 483, Inspection report pending |

**Review**

7. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

| | |
|---|---|
| Mid-Cycle Communication with Sponsor | 26-Feb-2018 |
| PeRC Meeting | 07-Mar-2018 |
| Late-Cycle Meeting Internal | 08-May-2018 |

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|---|---|
| Late-Cycle Meeting with Sponsor | 29-May-2018 |
| PMC Study Target | 31-Jul-2018 |
| Labeling Target | 31-Jul-2018 |

8. Establish a labeling review plan and agree on future labeling meeting activities.

   Action Due date: July 31, 2018

   Review Committee agreed to meet bi-weekly to discuss labeling. The first meeting will include all disciplines to determine scheduling and pairings. Subsequent meetings will only include 1 or 2 paired disciplines e.g. Clinical and Statistics; Pharm/Tox requested to go last.

**Confirm, as applicable**

9. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed. *[CMC Reviewer]*

   The CMC team is in the process of completing the task.

10. New facility information is included in the application, requiring implementation of regulatory job aid JA 910.01: Manufacturing Facility Data Entry If not complete, indicate date it will be completed. ***Is this applicable? [DMPQ CMC Reviewer].***

    Not Applicable; However, if there is a task related to this, Lori Peters will take on the responsibility.
    *Update- DMPQ confirms that the facility data entries are up to date and all pertinent facility sites are listed.

11. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan. ***[CMC Reviewer]***

    Not Applicable.

12. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid JA 900.01: Unique Ingredient Identifier (UNII) Code for additional information.

    The UNII code process was initiated on 2/8/18. Completion of this task is expected within 4 to 6 weeks.

13. PeRC presentation date is set for Wednesday, March 7, 2018 and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

    PeRC forms need to be sent to both Kay and Zuben by Wednesday, February 21, 2018.

14. **Action Items:**

    a. RPM to issue remainder information requests.

    b. RPM to send PeRC forms by Feb. 21 (2 weeks before Mar. 7 meeting).

15. **For applications subject to the PDUFA/BsUFA Programs:** ***[Review Committee Members, Management present at the meeting]***

    a. Reach agreement on information to be included in the Mid-Cycle Communication telecon with the Applicant (see section below).

    b. Reach agreement on dates for upcoming meetings such as the AC or Late Cycle Meeting.

       **Note:** the RPM may choose to pre-populate these dates prior to the meeting.

       i. Late Cycle Meeting - May 29, 2018
       ii. Advisory Committee: TBD
       iii. Labeling meeting to star Week of March 12th

## Mid-Cycle Communication Agenda/Summary

*A. This section is intended to be CBER's internal agreement of what will be discussed in the Mid-Cycle Communication (MCC) Telecon with the Applicant. The Review Committee should come to agreement on the following items.*

*i. The information should be completed in such a manner that it will serve as the basis of the Mid-Cycle Communication telecon agenda.*

1. Any significant issues/major deficiencies identified by the Review Committee to date.

a. Quality Control
    i. The method validation for the following assays is incomplete. The deficiencies are being communicated through second IR.
    (b) (4) Drug Product
        - Purity by (b) (4)
        - Quantitation of Histidine and Glycine by (b) (4)
        - Determination of Polysorbate 80 by (b) (4) method
        - Quantitation of Sodium and Calcium by (b) (4) (requires re-validation using product in this submission)
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    Drug Product
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    ii. Moisture determination: incorrect calculation formula in the method
    iii. Chromatography assay for (b) (4) : Insufficient validation

b. Pharmacology/Toxicology
    i. Ongoing Issue - A 26-week IV toxicity study in immune-deficient (b) (4) nude male rats, with a 26-week recovery interval, is ongoing. This study was requested by FDA in the May 31, 2017 Type B pre-BLA meeting. The applicant plans to submit an audited interim report containing all in-life data from all study animals and post-mortem data (including histopathology) from the animals sacrificed at the weeks 13 and 26 time points, in an amendment to the BLA by April 30, 2018, and a final audited report (to also include the 26-week recovery data) in the first quarter of 2019. The contents of the study report and possibly the date that the amendment is submitted will determine if it will constitute a Major Amendment to the BLA.

c. Epidemiology:
    i. We await the results of the ongoing, long-term (26 week) preclinical toxicity study in immune deficient male rats. This information will be required to enable full assessment of the submitted pharmacovigilance plan.

2. Information regarding major safety concerns.
    a. No major safety concerns have been identified at this time. The review is ongoing.

3. Preliminary Review Committee thinking regarding risk management.
    a. No comments at this time

4. Any information requests sent and responses not received.
    a. One existing CMC IR expected response on 2.16

5. Any new information requests to be communicated.
    a. No new information requests at this time.

6. Proposed date(s) for the Late-Cycle Meeting and the Late-Cycle Meeting Materials:

    The LCM is currently scheduled for May 29, 2018 from 1:00 PM to 2:00 PM ET.

    If these timelines change, we will communicate updates to the sponsor during the review.

7. Updates regarding plans for the AC meeting, if appropriate.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

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|---|---|
| Late-Cycle Meeting with Sponsor | 15-May-2018 |
| PMC Study Target | 31-Jul-2018 |
| Labeling Target | 31-Jul-2018 |