Mid-cycle Meeting, August 29, 2012 - Kcentra

125421/0 – Mid-cycle Meeting
August 29, 2012

Attendees:
Ze Peng (ZP)—Chair/CMC/Product
Beth Walton (BW)—RPM
La'Nissa Brown-Baker (LBB)—Pharm-Tox
Rebecca Olin (RO)—CMC/Facility
Tony Hawkins (TH)—BIMO
L. Ross Pierce (RP) and Nisha Jain (NJ)—Clinical
Sukhminder Sandhu (SS)—Epidemiology
Jiang (Jessica) Hu (JH)—Biostat
Lokesh Bhattacharyya and Karen Campbell (KC)—Lot Release
Kristine Khuc (KK)—APLB
Iftekhar Mahmood (IM)—Clinical Pharmacology

Not Present (CC):
Roman Drews (RD)—Consultant on CMC/Product
Anne Pilaro (AP)—Pharm-Tox
Amy Malla (AM)—Study Data Tabulation Model (STDM)

Purpose/Goals:

I. Information Request:

a. A comprehensive review and concurred memos are due by **9/13/12**
b. Goal to communicate issues/information request to the sponsor by **9/15/12**. Concurred Midcycle memos are due by **9/13/12**.
c. Epidemiology

II. Comments from Discipline Reviewers:

a. Epidemiology (SS):

- SS will communicate information regarding the breakdowns of the deaths noted by indication. The Applicant did not break down death by indication. The Applicant provided follow-up information on pharmacovigilance cases, but it was incomplete. FDA is awaiting response from Applicant.

b. Pharmacology (IM)

- The pharmacokinetic study of Prothrombin Complex Concentrate is acceptable (although of limited practical value since the study was conducted in healthy subjects). The Applicant should modify the clinical pharmacology labeling as suggested by the FDA.

c. CMC

- RO will send an IR to request extractable and leachables data on the resins, filters, and membranes used in the manufacturing process. DMPQ recommended waiving the manufacturing facility inspection. DMPQ may request **bioburden** testing information on the relevant manufacturing steps.

- ZP commented that CSL Behring provided information on the manufacture of 3 conformance lots of bulk drug substance (BDS) in this submission, ----------(b)(4)---------- conformance lots of final drug product (FDP) after sterile filling. These (b)(4) lots went through ---(b)(4)--- lyophilizers. The information on the lyophilizer(s) used for the intended U.S. market is unclear. ZP asked if DMPQ knows which lyophilizer(s) will be used for the manufacture of PCC for the U.S. market.

  RO noted that lyophilizer --(b)(4)-- is not for the manufacture of PCC for the U.S. market. We need to confirm the lyophilizer(s) used for the manufacture of PCC for the U.S. market (lyophilizers ----------(b)(4)----------).

d. Clinical

- Sponsor demonstrated non-inferiority of clinical homeostasis effectiveness, by the primary and secondary endpoints that were pre-specified.
- In terms of safety, in the pivotal clinical trial in acute major bleeding (RCT BE1116_3002), the ratio of deaths in the Beriplex (Kcentra) vs plasma group was 2:3. There were a total of 11 deaths noted in the Beriplex (Kcentra) group, more than twice as many as noted in the plasma control group (5).
- Still to be determined is whether we have sufficient data to ensure us that this product is not more toxic in terms of total mortality than plasma.
  Action: NJ will provide an independent analysis of death (timeframe TBD). Asked the Applicant to submit blinded narratives for all deaths for both the bleeding and ----(b)(4)---- phase 3 studies.
- Recommendation:
- There may be trends which show that Beriplex (Kcentra) may be more effective than plasma; however Beriplex (Kcentra) did not meet the criteria for superiority for clinical hemostasis (primary efficacy endpoint).
- It remains unclear why excess of deaths were observed in the bleeding study and not in the interim analysis of data from the surgery study. Still need to decide if Beriplex (Kcentra) is approvable with an appropriate pharmacovilgilence plan or if we will require more data from the ongoing surgery study before taking final action or we will ask them to do another study to obtain more robust data.
- Recommended granting the sponsor full waiver request for pediatric studies.

  Action:

- Identifying any issues that could prevent approval. Develop a clear plan for addressing any problems.
- Present at CBER Blood – RP recommended that we go to BPAC

e. **Epidemiology**

- The epidemiology review is still ongoing. Awaiting response to most recent IR to ensure the database for spontaneous reports is accurate and complete.
- Main concerns from an epidemiology perspective are the completeness of data that would be gathered across two cohorts (Kcentra and plasma) in the applicant's proposed active surveillance study, and whether there may be bias in the two

cohorts that cannot be adequately addressed via matching. Also, there is concern if the feasibility study fails, the imbalance of deaths and in treatment-emergent AEs, possible differential loss to follow-up and medical chart review on only 50% of TEE cases are areas of concern.

- The epidemiology and clinical reviewers wanted to make sure that the cohort recruited has an indication of reversal of VKA anticoagulation. In response to an earlier IR, the Applicant provided a revised PVP, but FDA has submitted another IR for the Applicant to be more explicit regarding the indication and other details of the proposed PVP epidemiologic cohort study.

f. **BIMO** – Submitted midcycle review Aug 7th. The reviewer does not see any "show stoppers" at this point. There are a few 483 items that appear minor on cursory examination.

g. **STAT**

- Still reviewing primary endpoints and secondary endpoints. Still determining whether any theoretical advantage of Beriplex (Kcentra) is translating to a clinical advantage, based on the data.
- This statistical reviewer verified the Applicant's efficacy result of the proposed product provided in the study results of BE1116_3002 [using the Applicant-supplied analysis datasets]. The study BE1116_3002 results meet the pre-specified non-inferiority criterion (compared to plasma) for both the primary and co-primary efficacy endpoint. Safety analyses and subgroup analyses are also reviewed but incomplete at this moment. Currently, no major statistical concerns on the efficacy of the study BE1116_3002 have been identified.
- If the submission goes to BPAC, then the Applicant could be asked about their safety outcomes, especially the higher mortality in the PCC treatment group. For the efficacy outcomes, the Applicant could be asked the under power problem of the pivotal trial in acute major bleeding.

i. Pharm-Tox – Labeling concerns will be discussed with Ross.

III. Labeling

- Labeling Meetings will need to be tentatively scheduled at the end of September 2012.
- Planning to send labeling comments to the applicant around December 14, 2012.
- Question: Should the statistician review previous labeling changes? RP noted that given that the Applicant did not adjust their P-value, the FDA statisticians could recommend the Applicant to omit certain labeling or offer suggestions on labeling changes.
  Action: RP: We will want to present the confidence interval for 45-day mortality. Statisticians would like to clarify the "ITT-S" (Intention-to-treat for Safety) and "ITT-E" (Evaluable-for-efficacy) and clarify the Applicant's definitions.
  Action: IM will send RP labeling changes to send to the Applicant.

IV. BPAC

- The team needs to make recommendations for review to go to advisory committee shortly after the mid-cycle meeting.

- BPAC waiver is required if the committee decides not to go to BPAC.
- RP recommended that we go to BPAC.

V. PeRC

- If orphan status is granted, PeRC presentation is not required.

If the Applicant does not receive Orphan Drug status – the Applicant can ask for waiver for pediatric studies. The clinical group agrees with granting full waiver of pediatric studies. Agree with the Applicant that those cases are rare and it would take decades to conduct an adequate pediatric efficacy study.

VI. Lot Release.

- Lot release meeting was held on 7/31/12.
- Lot release testing will occur at the end of September 2012.

VII. PMRs/PMC

- There will be discussion for a potential PMR.

VIII. PREA. Wei: Pediatric population in the Phase IV, PMR: We will not be requesting a phase IV pediatric study; they requested a waiver.

IX. Press Release: **Due by 1/14/12 (**

X. Summary Basis for Regulatory Action (SBRA). Due 30 days before approval to Jay Epstein (Due Date: **12/29/12**). Executive summary from each review discipline is required by **12/14/12.**