Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

MEMORANDUM ADDENDUM

Date:	Feb 18, 2015
From:	Bethany Baer, MD Medical Officer, Pharmacovigilance Branch (PVB), Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE)
To:	Chava Kimchi-Sarfaty, Chair of BLA 125426 Review Team, Office of Blood Research and Review
Through:	Christopher Jankosky, MD, MPH Branch Chief, PVB, DE, OBE David Martin, MD, MPH Director, DE, OBE
Subject:	Review of BLA Resubmission 125426/0.39. Memorandum addendum to Pharmacovigilance Plan version 2 review memo written on May 27, 2014.
Applicant:	Cangene/Emergent BioSolutions
Product:	Recombinant Factor IX Concentrate, Ixinity (IB1001)
Proposed Indication:	Control and prevention of bleeding, peri-operative management in patients with hemophilia B, and secondary, tertiary, or intermittent prophylaxis to reduce the frequency of bleeding episodes in adults and children ≥12 years of age with hemophilia B.
Submission Type:	BLA 125426/0.39
Submission Date:	Oct 28, 2014
Action Due Date:	Apr 29, 2015

1. INTRODUCTION

a. Product Description

Coagulation factor IX (Recombinant), IB1001 (also referred to as Ixinity), is a purified recombinant form of the human coagulation factor IX protein. It is produced in Chinese Hamster Ovary (CHO) cells and is a single chain glycoprotein with an amino acid sequence identical to the Thr148 allelic form of plasma-derived factor IX. It is used to treat patients with hemophilia B. It is functionally and structurally similar to BeneFIX (a recombinant factor IX currently marketed in the United States), and would provide an alternative to the factor IX products already approved in the U.S. Following a Complete Response letter in 2013, the sponsor added a (b)(4) step to the manufacturing process (referred to as the "modified process") to remove host cell proteins (HCPs). The sponsor refers to the product that has undergone the modified process with the (b)(4) step as the "polished" product.

b. Regulatory History

The study IB1001-01 under the IND 13551 was placed on clinical hold by the FDA on July 5, 2012 due to concerns regarding the development of anti-Chinese hamster ovary protein (CHOP) antibodies in 18 of 68 subjects in the trial.[1] Subsequently, the initial application for licensure was issued a Complete Response (CR) letter on Feb 1, 2013. The Division of Epidemiology (DE) reviewed the initial application for IB1001 in a memo dated Dec 12, 2012. The Complete Response letter listed 25 comments, of which 16 were related to Chemistry, Manufacturing, and Controls issues. The main concern from the review team centered on the level of CHO proteins and the associated immunogenicity. Following the addition of the (b)(4) step to remove host cell proteins, the clinical hold was lifted on IND 13551 on Jul 26, 2013.

On Jan 27, 2014, the sponsor (now Cangene/Emergent BioSolutions instead of the original sponsor, Inspiration Biopharmaceuticals) resubmitted the application with responses to the CR letter, an updated IB1001-01 study report with a data lock date of Mar 1, 2013, an updated summary of clinical safety, and a new pharmacovigilance plan. The BLA was issued a second Complete Response letter on Jul 29, 2014 due to CMC and inspection concerns. The sponsor responded to the second CR letter on Oct 28, 2014 with this current submission.

c. Objectives

This memorandum addendum is in response to a request from the Office of Blood Research and Review (OBRR) to the Office of Biostatistics and Epidemiology (OBE) to review the BLA resubmission received as 125426/0.39 on Oct 28, 2014. There is not a new PVP with this resubmission as PVP version 2 received Jan 2014 is still applicable. This submission contains several updates on patients in the ongoing clinical studies which will be reviewed in this memo addendum.

[1] IND 13551, FDA Clinical Hold Letter, dated Jul 5, 2012

2. MATERIALS REVIEWED

Source	Subtype	Document Reviewed
Cangene	BLA 125426/0.18	Pharmacovigilance Plan Version 2.0
Cangene	BLA 125426/0.32	Cover Letter (contains updates on Studies IB1001-03 and IB1001-04)
Cangene	BLA 125426/0.39	Summary of Clinical Safety (resubmission with data lock date of Mar 1, 2013)
Cangene	BLA 125426/0.39	Immunogenicity Risk Assessment, IB1001, dated Oct 27, 2014
Cangene	BLA 125426/0.42	Immunogenicity Risk Assessment, IB1001, dated Dec 16, 2014
FDA	IND 13551	Clinical Hold Letter, dated Jul 5, 2012
FDA	Review Memo	Division of Epidemiology Pharmacovigilance Plan Version 0.1 review by Bethany Baer, MD, dated Dec 12, 2012
FDA	Review Memo	Division of Epidemiology Pharmacovigilance Plan Version 2 review by Bethany Baer, MD, dated May 27, 2014

3. PHARMACOVIGILANCE PLAN REVIEW

The Pharmacovigilance Plan Version 2 was received on Jan 27, 2014 and reviewed in a DE memo in May 2014. This current BLA resubmission does not include a new PVP and thus, the PVP version 2 is still applicable. Please see the May 27, 2014 DE memo for a review of the PVP Version 2 including the safety specifications and the sponsor's proposed actions. In a cover letter submitted prior to the response to the CR letter, the sponsor notified the FDA of their plan to discontinue planned Study IB1001-03 before it is initiated.[2] This study was to evaluate Ixinity in previously untreated patients (PUPs) who were <6 years of age. In the letter, the sponsor stated that these types of studies in PUPS are no longer required in Europe for products that are not novel so the sponsor is no longer planning to conduct the study. The sponsor also provided the update that Study IB1001-04 is currently on internal hold pending the sponsor's strategy in Europe. These updates affect the PVP version 2 by removing Study IB1001-03 but retaining Study IB1001-04. No changes were stated for Studies IB1001-01 and IB1001-02.

4. UPDATE ON IB1001 CLINICAL DATABASE

This resubmission includes updated Immunogenicity Risk Assessment Reports dated Oct 27, 2014 and Dec 16, 2014 which provide additional information on patients in studies IB1001-01 and IB1001-02. This report contains available safety data up to Jul 17, 2014 for IB1001-01 and Oct 24, 2014 for IB1001-02. As of those data lock dates, there were 17 subjects in IB1001-01 and 7 subjects in IB1001-02 who had transitioned to the polished product. Of the 17 subjects in IB1001-01, all 10 of the anti-Chinese hamster ovary protein negative subjects remained negative. Two of the anti-CHOP positive subjects had decreasing titers on polished IB1001 and two other anti-CHOP positive subjects have not had long enough follow-up on the polished product to determine response (results only available after 5 exposure days). The 3 subjects who were indeterminate for anti-CHOP status continued to be indeterminate.[3]

For the pediatric study IB1001-02, anti-CHOP testing was not conducted at baseline study entry as the study began prior to the implementation of anti-CHOP testing for the IB1001-01 continuation phase. Three of the 9 subjects tested positive for anti-CHOP

[2] BLA 125426/0.32, Cover letter.
[3] BLA125426/0.42 Immunogenicity Risk Assessment, p. 9.

after receiving the unpolished IB1001 product. One additional subject had 2 positive results for anti-CHOP while receiving a different marketed FIX product for 3 months after stopping IB1001. All 3 of the positive anti-CHOP subjects in this study had decreasing anti-CHOP titers after transitioning to the polished product.[4]

Unchanged from the data available at the time of the Jan 2014 submission, a total of 20 (29%) of 68 subjects have been documented to have anti-CHOP seroconversion in study IB1001-01. An additional 11 subjects had indeterminate results, including two subjects who were positive at baseline. A seroconversion rate was not available for study IB1001-02 because baseline levels were not tested. There have been three (33%) of nine patients in IB1001-02 who have tested positive for anti-CHOP during the study. In assessing any associated adverse events or laboratory studies, there has not been a safety concern. This includes patients who have been followed for up to three years on IB1001.[5]

Of note, the manufacturer introduced a new (b)(4) test for anti-CHOP to use in addition to their anti-CHOP assay. The sponsor states that the new (b)(4) assay is more process specific and will be implemented after further validations.

Regarding inhibitory anti-factor IX antibodies, as of the December Immunogenicity Risk Assessment Report, there continued to be no inhibitory antibodies to factor IX at any time point during the 2 studies. These results included 62 subjects on prophylaxis in study IB1001-01 and 9 subjects on prophylaxis in study IB1001-02. There were also no cases of anaphylaxis or nephritic syndrome seen in any of the subjects.[6]

The update on non-inhibitory anti-factor IX antibody results showed that two additional subjects in IB1001-01 tested positive. In total, there were 23 (30%) of 77 subjects who showed the presence of non-inhibitory antibodies to factor IX during the study. Of these 23 subjects, 5 were positive at baseline. The remaining 18 patients had primarily sporadic test results when evaluated for the non-inhibitory factor IX antibodies. Formation of these antibodies did not appear to be associated with formation of anti-CHOP, lack of efficacy of factor IX, or adverse events.[7] In study IB1001-02, three (33%) of the nine patients were positive for non-inhibitory anti-factor IX antibodies. One of the three subjects was positive for anti-CHOP as well. The positive tests in these three patients were all transient. Two of the subjects had a single positive test and one subject had three positive tests. All three of the subjects had subsequent negative tests. The transiently positive tests did not appear to cause an adverse event.[8]

5. INTEGRATED RISK ASSESSMENT

This updated clinical information does not change the overall benefit-risk of IB1001. The Pharmacovigilance Plan Version 2 continues to outline appropriately the safety specifications and postmarketing monitoring plan for IB1001. Initially, the primary

[4] BLA125426/0.42 Immunogenicity Risk Assessment, p. 16-17.
[5] BLA125426/0.42 Immunogenicity Risk Assessment, p. 25, 32.
[6] BLA125426/0.42 Immunogenicity Risk Assessment, p. 19.
[7] BLA125426/0.42 Immunogenicity Risk Assessment, p. 20.
[8] BLA 125426/0.39, Immunogenicity Risk Assessment, p. 27.

concern regarding IB1001's safety was the unknown significance of antibody formation in a high percentage of trial subjects. With the updated data available in this submission, there was a seroconversion rate of 29% of clinical study patients developing anti-CHOP antibodies. Additionally, 30% of subjects tested positive for non-inhibitory factor IX binding proteins during the study. As stated in the May 2014 DE review memo, **i**n response to the anti-CHOP antibodies, the sponsor made a manufacturing change to decrease the residual CHO protein in the product, and a pharmacokinetic comparability study was performed. Neither of these antibodies was found to be associated with adverse events, including hypersensitivity reactions or inhibitor formation. This resubmission included additional follow-up on patients who had tested positive for anti-CHOP antibodies and provided some reassurance that no clinical adverse events were found to be associated with the longer observation period. Additionally, it showed that titers of anti-CHOP antibodies decreased over time in the majority of patients. The sponsor confirmed that there were lower levels of CHO protein in the polished product, and there is some limited data available to demonstrate that this may result in fewer patients developing anti-CHOP antibodies. Information regarding the non-inhibitory FIX binding antibodies and the anti-CHOP antibodies seen in the clinical trials has been included in the draft labeling.

While there is still very limited clinical data on the polished product, the available data on the outcome of patients with anti-CHOP antibodies and non-inhibitory factor IX binding antibodies is reassuring. Multiple other factor replacement products have been found to have antibodies of unknown significance associated with them. Some of these products continue to have specific antibody testing as part of ongoing clinical postmarketing commitment studies. The approach of monitoring the development of anti-CHOP antibodies, factor IX inhibitors, and non-inhibitory factor IX binding antibodies in the 3 ongoing and planned studies is acceptable. There has been no demonstrated clinical effect of anti-CHOP antibodies. Additionally, the mechanism for removing the host cell antigenic material is expected to be effective, and there was a demonstrated decrease in anti-CHOP seroconversion in animal models. There was no demonstrated clinical effect of anti-factor IX binding antibodies, and no correlation with developing inhibitors. Throughout the clinical trial, there were no inhibitors observed, and this product is not expected to have a higher rate of inhibitor development than approved similar factor products. Therefore, the reviewed safety data do not substantiate a need for a safety PMR or a risk evaluation and mitigation strategy (REMS).

6. RECOMMENDATION

The pharmacovigilance plan Version 2 is acceptable. It is understood that Study IB1001-03 is no longer part of the Pharmacovigilance Plan. There are three ongoing and planned studies which will provide additional safety and efficacy information for this product.